BEHAVIORAL CONTROL OF SEIZURES IN SQUIRREL MONKEYS (SAIMIRI SCIUREUS)

A Thesis

Presented to

The School of Graduate Studies

Drake University

In Partial Fulfillment

of the Requirements for the Degree

Master of Arts

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by

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August, 1976

BEHAVIORAL CONTROL OF SEIZURES

IN SQUIRREL MONKEYS (SAIMIRI SCIUREUS)

An Abstract of a Thesis by
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August, 1976
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Problem: to ascertain whether epileptic seizures develop as a result of a laboratory produced lesion of the nodosa ganglia of the vagus nerve, to condition the inhibition of seizures, and to theorize on sudden death.

Procedures: eleven Squirrel monkeys were surgically implanted with depth electrodes. Electroencephalographic recordings were made and 38 days later lesions of the nodosa ganglia were created. Seizures were punished with electro stimulation and desirable behavior was positively reinforced.

Findings: the lesion of the nodosa ganglia of the vagus nerve created seizures which were suppressed with punishment-differential reinforcement of desirable behavior.

Conclusions: it is possible that a vagal lesion is the explanation of the sudden death of persons diagnosed as epileptic, of persons who are not diagnosed as epileptic but who have disruptions of cardiac or respiratory functions, and of young babies, classified as crib deaths, who have the same cardiac and respiratory failure.

Recommendations: further research is needed.

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CHAPTER I

INTRODUCTION

Little is known about the unexpected deaths of relatively young persons ranging from a few months of age into the third decade of life. Based upon an autopsy report (Webb, 1969), a young 32 year old woman began having clonic, tonic, epileptic seizures with no known record of disease or accident. The medical history during approximately three months included several complete physical examinations, electrocardiograms, electro-encephalograms and laboratory work. No irregularities were detected in any of these evaluations. The physician witnessed the fatal episode. After her death, the physician stated that he had researched the matter but admitted that he could not explain or fully understand the seizures or the death. The pathologist listed the cause of death as acute pneumonitis. This represented conditions existing at the time of death. Two other findings were severe myocardial fibrosis, the heart muscle was being replaced by tissue similar to scar tissue although this condition did not appear in chest x-rays or on the electrocardiogram, and severe chronic thyroiditis, the thyroid gland was also being replaced by the same type of scar-like tissue and this condition was not indicated by tests or other clinical evidence. Nothing abnormal was detected in the brain.

A comprehensive study was made by the Coroner's Office, Cleveland, Cuyahoga County, Ohio, of the unexpected

death in young epileptics. The deaths occurred from 1950 to 1969, included 58 persons between the ages of six and thirty years, and all had been diagnosed as epileptic. Clinical histories of 19 persons were located. Most of these patients had clinically mild epilepsy of long duration. Eight of the 19 fatal episodes were witnessed, and in four, death occurred suddenly without manifestations of a motor seizure except for a brief tonic phase in two patients. Satisfactory anatomic causes of death were not established in any patient. "Pathophysiologic mechanisms of death due to uncomplicated epilepsy appear to relate to acute disruptions of brainstem cardiac or respiratory functions or both as a consequence of seizure discharge" (Hirsch & Martin, 1971, p. 689).

An epileptic seizure is a state produced by an abnormal excessive neuronal discharge within the central nervous system and is a symptom of a disease (Penfield & Jasper, 1954). Gibbs and Stamp (1958) define epilepsy as a "disordered regulation of energy release within the brain" (p. 3). They consider that the seizure is but a small manifestation of the larger, hidden picture. The informative hidden part which goes on inside the patient is the flow of energy which is improperly timed and spaced within the brain.

The contributions of John Hughlings Jackson (1931) are the foundations for the modern study of epilepsy. He considered a discharge of unstable cells in the lesion

leads to a secondary discharge of healthy cells in other centers, which is the focus. Jackson's approach to convulsions was to determine the discharging lesion and the pathological process which caused it, not to ascertain if the episode was epilepsy.

Hess (1949) reported that numerous responses of various segments of the autonomic nervous system have been elicited by local electrical stimulation in the diencephalon. These responses include pupillary dilatation, salivation, piloerection, and sham rage, elicited principally from the hypothalamus. Lezhava (1973) utilized photic stimulation to evoke seizures and noted that stimulation of the vagus nerve increased the flow of afferent impulses, indicating an etiological and pathogenic factor in epilepsy.

Other phenomena which may accompany major seizures involving the diencephalic autonomic seizures are urination, vasomotor change in which there is an alteration in pulse rate and in blood pressure, flushing and pallor, erhythema, frothing at the mouth, and momentary loss of consciousness (Penfield & Jasper, 1954).

The autonomic nervous system includes the sympathetic and parasympathetic nervous systems. These two systems function as antagonists, exciting and inhibiting visceral organs. The two systems normally function in a homeostatic manner, checking and balancing each other.

The heart and lungs are innervated by the autonomic system. The heart rate is determined by the sino-auricular

node. The natural rhythm is controlled by the antagonistic inhibition and excitation by innervation from the vagi, a cranial nerve (parasympathetic) and the cardiac acceleratory nerve (sympathetic) (Adelson, 1953).

The vagus nerve has one sensory and two motor nuclei in the medulla and also has the most extensive distribution of any cranial nerve. Its roots are located in a postolivary position in the medulla in the postero-lateral sulcus. They exit from the cranial cavity via the jugular foramen.

The dorsal motor nucleus of the vagus nerve forms the vagal trigone on the floor of the fourth ventricle and the upper one-third of this nucleus provides preganglionic parasympathetic innervation to the ganglion in the lungs and heart. The other motor division of the vagus nerve originates from the posterior two-thirds of the ambiguus nucleus in the medulla and the upper one-third sends parasympathetic innervation to the following muscles: the superior, middle and inferior constrictors of the pharynx, the palatoglossus, palatophyaryngeus, salpingo-pharyngeal, and the levator palatine valum of the soft palate, the posterior cricoarytenoid, arytenoid, lateral cricoarytenoid, and the thyroarytenoid of the larynx.

The primary cell bodies of the sensory fibers are located in the inferior ganglion and carry gustatory information from taste buds in the epiglottis and pharynx, cutaneous innervation from the base of the tongue and

epiglottis, and general visceral sensation from all the structures receiving motor innervation. The fibers enter the medulla and synapse in the nucleus solitarius. The secondary axons ascend in the medial lemniscus to the ventroposterior thalamic nuclei (Curtis, Jacobson, & Marcus, 1972).

The left and right vagal innervation are not identical (Holt, 1968). Adelson (1953) states that stimulation of the right vagus nerve slows the atria and ventricles, decreases atrial contractions, increases contractions of the ventricles diastolic dilatation of the heart. Some fibres of the right vagus terminate in the sinoauricular node, decreasing the rate of discharge. Stimulation of the left vagus nerve slightly slows the atria and ventricles, resulting in heart block. This indicates that fibres from the left side innervate the atrioventricular node. Strong stimulation of both vagi slows the atria, decreasing the contractions. This results in complete heart block with idio-ventricular rhythm and a slow feeble beat. Inadequate coronary blood supply and myocardial anoxia are a result of feeble cardiac contractions. Death results if asystole or ventricular fibrillation supervene.

Wolf (1968) believes that it is more likely that the vagus nerve and the sympathetic system are not solely antagonistic, but that they often function cooperatively to produce purposeful patterns of body reaction which may

be a "means of death rather than a cause of death" (p. 159). He refers to this as a "diving reflex" and postulates, "Central neural connections of the autonomic system are important in the production of potential arrhythmias, with or without injury to the heart. That such a potentially lethal central excitatory state may be damped or blocked by the regulatory (and potentially life-saving) effects of an inhibitory mechanism" (p. 159). He makes reference to Pavlov's classical conditioning studies on inhibition of autonomic function as an example of learned inhibition which may be self-destructive.

Lesions of the vagal nuclear complex seldom appear in scalp or cortical electrodes and are accompanied by tonic, clonic seizures which are usually fatal. Such lesions are difficult to diagnose even in autopsy. This is exemplified in the two introductory studies. According to Penfield and Jasper (1954), a lesion incurred at birth may not appear until the third decade of life.

The most successful method yet developed for the experimental production of focal epileptogenic lesions in monkeys is by local application of alumina cream (a colloidal precipitate of ammonium hydroxide and ammonium alum). Jasper (1972, p. 585) states alumina cream meets the criteria of validity for an epileptic lesion. These criteria are prolonged, spontaneous, recurrent seizures accompanied with electrical manifestations.

Chronic epileptogenic lesions produced by the injection of alumina cream into subcortical areas in monkeys may cause severe convulsive seizures to develop (Kopeloff, Whittier, Pacella, & Kopeloff, 1950). Alumina cream has also been effectively utilized to create foci in spinal neurons which exhibited many of the physiological properties of epileptic neurons in cortical foci (Kennard, 1950a, 1950b, 1953). Disadvantages of using alumina cream are latency prior to development of focal seizures, significant tissue destruction, and inconsistent effectiveness on all neural tissue (Ward, 1972, p. 13-35).

The electro-chemical theory of synaptic transmission assumes that transformation of chemical energy into electrical energy is a basic life process, a constant activity of all cells. The electrical signals are manifestations of complex systematic physical and chemical processes which create potential differences between the interior and exterior of the cell and between different portions of its surface, creating electro-chemical characteristics which include the electrical signals, and properties of the membrane such as resistance, capacitance, and permeability; and compartmentalization of ions and their passage between compartments. Current flow is directly affected by the factors that determine ionic mobility (Kooi, 1971).

The activation of nerve cells that results in electrical phenomena are detectable by electroencephalo-

gram. A slow-wave, described as bipolar negative-positive, has been identified as the precursor to epileptic seizures (Wyss, Frankhouse, & Crowell, 1968). During the early phases of seizure development, Wyss et al., discovered that the wave form characteristically began with a negativity of approximately 700 uV with a duration of about 200 mSec. This negativity was followed by a positive deflection of 200 uV for 500 mSec. The results of their study indicated that these precursor waves were part of the epileptic focus.

Chemical imbalance within the brain, especially hypoglycemia and hypocalcemia, have been shown to cause epileptic seizures. Thyroxytropin, which is released by the pituitary, interacts upon the thyroid. The thyroid determines the calcium level, which reacts with the parathyroid. The parathyroid regulates the blood calcium level. Thyroxin released from the thymus affects the levels of nerve growth factor serum, calcium and uric acid. The thymus releases thymosin, which affects the antibodies and natural immunity. Nerve growth factor serum has been correlated with regeneration and the familial disease, Riley-Day syndrome (Aguayo, Martin, & Gray, 1972), and electroencephalographic patterns and depression (Fader & Struve, 1972). This information is relevant, considering that the thyroid is innervated by the vagus nerve.

All epileptic processes have the same fundamental properties with apparent differences in clinical and

electrographic differences being due to the functional characteristics of the neuronal circuits participating in the epileptic discharge and the physical changes in the focus, i.e., the electroencephalograph and behavior may take different forms as a lesion changes and still be indicative of epilepsy.

Subdivision of the epilepsies is possible by the study of the clinical patterns of attacks (Gibbs & Gibbs, 1964; Gibbs & Stamp, 1958). However, it is impossible to adhere strictly to such classifications. The initial phenomenon of any seizure is the most important localizing feature of the attack. The evolution of the clinical symptoms often helps to understand the location of initial discharge and this may assist in identifying the focus where the discharge is occurring. A local discharge in any area of the brain may produce a secondary discharge in another location, a mirror focus. In major convulsive seizures, discharge eventually involves the gray matter of the subcortical coordinating system, the centrencephalic system and may involve the cortical gray matter of both hemispheres. It can then be expected that the same type of local discharge can occur in the gray masses of the brainstem. Local irritative seizures involving the cranial nerves in the posterior fossa have been described in cases of posterior fossa tumor by Stewart and Holmes (1904) and by Mills and Weisenberg (1914).

Consideration of behavior, whether it be seizures or learning, must involve the entire organism. The higher the phylogeny, the more complex the nervous system and behavior.

Learning is a relatively permanent change in behavior over time of practice or experience and is dichotomized by two major types of learning: classical conditioning and operant conditioning. Classical conditioning is a process in which a respondent is elicited by an unconditioned stimulus preceded by a conditioned stimulus. The subject's eventual response to the conditioned stimulus does not affect the occurrence of the unconditioned stimulus. Operant conditioning is a process in which the frequency of emitting a response is modified by its consequences. The experimenter attempts to control the environment, manipulates independent variables and studies the effects upon the dependent variable, the behavior.

According to some theorists (Skinner, 1938; Mower, 1947; Kimble, 1961), classical conditioning involves the autonomic nervous system and operant conditioning involves the somatic nervous system. Recent research refutes this position. The neural electrical activity of the brain is considered an autonomic response and Olds (1969) increased and decreased the rate of firing of a single cell in the fimbria by reinforcing spontaneous firing by electrical stimulation of the medial forebrain bundle. Miller (1969) demonstrated that both striated and smooth muscle,

glandular responses, heart rate and blood flow were conditionable either by classical or instrumental paradigms. Wyrwicka and Sterman (1968) demonstrated that the spontaneous occurrence of a 12-20 c/sec. slow wave spindle in the sensory motor cortex was increased by its reinforcement with milk given to the animal. Delgado, Johnston, Wallace, and Bradley (1970) conditioned amygdala spindling through contingent stimulation of a pleasure and punishment center of the brain, demonstrating an increase and decrease of spindling. The findings of Delgado, Roberts, and Miller (1954) indicate that electro stimulation of the ventral posterior nucleus of the thalamus enhanced learning. The results of the studies cited above indicate that the technique of operant conditioning lends itself to many therapeutic possibilities, including epileptic seizures.

Learning may be either a relatively permanent increase in behavior or a relatively permanent suppression in behavior. Some methods of suppression of undesirable behavior are the utilization of positively reinforcing differential rates of other behavior, punishment, or a schedule combining both punishment and reinforcement: punishment-differential reinforcement of other behavior.

Much uncertainty exists regarding the effects of punishment. Church (1963) defined the punishment procedure as "one in which a noxious stimulus is contingent upon the occurrence of a response" (p. 370). The

effectiveness of punishment is not only questioned, but other processes have been utilized to explain its effectiveness, such as passive avoidance, which assumes that punishment itself is ineffective but sets the occasion for responses which are incompatible with the punished response. Punishment has also been indirectly defined in terms of a negative reinforcer (Catania, 1968).

Recent studies have been made to study the phenomenon of punishment as a fundamental behavioral process. The conditions for maximum effectiveness of punishment are: (1) No unauthorized escape responses should occur, (2) The stimulus should be intense and delivered immediately after the occurrence of the specified undesirable response, (3) The frequency of the punishing stimulus should be high, ideally following every response, (4) Motivation level should be low, i.e., deprivation should be low and the amount of the reinforcer maintaining the behavior should be small, (5) An alternative response should be available, is never punished, and is actually in competition to the undesirable response, and (6) A period of extinction rather than reinforcement should follow the punishing stimulus (Williams, 1973).

Just a punishment has been utilized to reduce or eliminate response rate, positive reinforcement schedules have been used to reduce response rate. Differential reinforcement of low rates of response

and differential reinforcement of other behavior are two schedules of positive reinforcement utilized to decrease response rate.

Zeiler (1970) studied other behavior as a consequence of reinforcing not responding. He contends that there is no data which show that differential reinforcement of other behavior schedules does condition other behavior when they succeed in decreasing the frequency of a specified response. He discusses the problem of identifying the behavior after it develops, measuring and manipulating it. He posits the solution: "Structure the situation so that the hypothesized adventitiously reinforced response may be specifiable in advance. If a response is already occurring at a substantial frequency, it is likely to be present when reinforcements occur and should maintain or increase its frequency through the consequent, albeit accidental, correlations with reinforcement" (p. 149). Zeiler (1971) also studied elimination of behavior with reinforcement. He concluded that differential reinforcement of other behavior reduced response rate faster than did extinction and spontaneous recovery occurred only during the stimulus associated with extinction.

Holz and Azrin (1961) studied the methods of punishment, satiation, extinction and stimulus change in reducing the response rate. They concluded that

punishment produced an immediate, complete, enduring effect in response reduction. Punishment reduced the short interresponse times and increased the frequency of long interresponse times, increasing the efficiency of the differential reinforcement of low responding because the animals received reinforcement more often. Sears, Macoby, and Levin (1957) state that combining punishment with positive reward of some alternative response is more effective than just punishment. Church (1963) also expresses a similar opinion: punishing one response and reinforcing an incompatible response is an effective method of suppressing behavior.

Combining schedules of punishment-differential reinforcement of other behavior schedules appears to be the most effective and enduring method to suppress undesirable behavior and to encourage desirable behavior. This schedule maximizes the six requirements for effective punishment procedures and appears to be adaptable to effectively suppress epileptic seizures and encourage other, more adaptive behavior. The reinforcement would condition the adaptive behavior. The punishment would suppress the undesirable behavior.

The purpose of this research is to study the effects of a vagal lesion, to ascertain whether behavioral manifestations and electroencephalographic patterns of autonomic epileptic seizures develop, can be suppressed

by using a schedule of punishment-differential reinforcement of other behavior, and to theorize on sudden death. Because of the curvature of the brainstem in humans, it is necessary to use other primates which correlate anatomically with humans. The size and handling ability of Squirrel monkeys makes them amenable to laboratory research and are used in this study.

CHAPTER II

METHOD

Subject

Eleven Squirrel monkeys (Saimiri sciureus), approximately one and one-half years of age, weighing between 400 to 600 grams, and purchased from Primate Importing Corporation, New York, New York, were used in this study. Their country of origin was Peru.

Each animal was housed in a cage one foot by two feet by two feet. The cages were placed in a rack, which held two rows of five cages. The colony room dimensions were eight feet by 16 feet with nine foot ceilings. Air entered through a ceiling inflow duct. The temperature of $75^{\circ} \pm 5^{\circ}$ was maintained by an electric thermostatically controlled room heater. Relative humidity of 30 to 35% was maintained with a Westbend Room Humidifier operated at maximum output 24 hours per day. Light was artificial and consisted of electric, flourescent ceiling lights centered and running the length of the room. The lights were automatically turned on at 7 A.M. and turned off at 9 P.M. daily. Each subject received Waynes Monkey Chow and water ad libitum and were never deprived.

Surgical Technique

Sterile procedure was used and the assistants were certified medical technicians. Under Ketaset anesthetic (Veterinary Products, Bristol Laboratories, Division of

Bristol-Myers Company) injected intramuscularly, each subject was implanted with stainless steel depth electrodes. A dental drill was used to effect the holes in the skull. Electrode coordinates were determined from Gergen and MacLean's atlas (1962). Electrode placements were made with a stereotaxis. The electrodes were purchased from Rhodes Medical Instruments. A monopolar electrode was implanted into the hippocampal commissure (Fr. 4.5, Lat. Left 2.5, H. 14.45). A monopolar electrode was implanted into the corpus callosum (Fr. 4.5, Lat. Left 3.5, H. 11.7). A bipolar electrode was implanted into the ventroposterior nucleus of the thalamus (Fr. 9, Lat. Left 5.5, H. 15.7). A bipolar electrode was implanted into the solitary nucleus (Fr. 1, Lat. Left 1.1, H. 27.6).

Six stainless steel screws, size 1/16 x 1/8 inch, to which Driver-Harris wire was soldered, were implanted through the skull. The meninges were broken and the screws inserted to touch the dura in the right and left frontal, right and left parietal, and right and left temporal areas to record cortical activity. Two screws were placed into the left and right frontal sinuses to serve as the ground and reference electrodes. Each electrode and cortical screw were secured to the dry skull with dental acrylic. After all electrodes and screws were secured, the wire leads were soldered into a 14-lead, blue ribbon, amphenol skull plug obtained from Allied Electronics.

For three days following surgery, each subject received .25 cc daily injections of Bio Delta. Five animals became deceased within two postoperative days and one animal died the 28th postoperative day.

One subject with only electrode implantation served as the control. Two subjects received bilateral alumina cream (Amphojel) injections (.05 cc) into the nodosa ganglia of the vagus nerve 38 days after electrode implants. Under Ketaset anesthetic and using sterile procedure, incisions were made through the skin on the dorsal side of the neck adjacent to the spinal column. Using mosquitoe forceps, the neck muscles were separated for entrance to the vagus nerve as it exits from the skull through the jugular foramen. Using a syringe with a 27 gauge needle, .05 cc of alumina cream was injected bilaterally into the nodosa ganglia. The incision was then sutured.

Two subjects received bilateral blunt dissections of the nodosa ganglia of the vagus nerve 38 days after electrode implants. Under Ketaset anesthetic and using sterile procedure, incisions were made through the skin on the dorsal side of the neck as described above. After separating the neck muscles for entrance to the vagus nerve, a gall bladder forcep was placed around the nodosa ganglia and a micrometer was then placed upon the forcep, turned 75 millimeters, and held 75 seconds before being removed. The incision was then sutured.

Apparatus

The recording cage (Farrady cage) consisted of a one foot by two foot by two foot galvanized, woven wire cage, the floor of which was covered by a piece of wood ½ inch by 18 inches by 10 inches and covered with a linen towel.

On top of this cage and mounted upon a wooden frame was a 14 inch by 14 inch slip-ring made of Plexiglas. Carved in the top of the Plexiglas were 14 shallow, circular grooves, evenly spaced and filled with mercury. Fourteen recording needles, attached to a rotating arm, floated in the mercury. Attached to the posterior end of the slip-ring cable was a female amphenol connector which attached to the male amphenol plug on the subject's skull. The cable exiting from the slip-ring contained 14 plugs which connected to the panel box of the Model III Grass Electroencephalography. The recording cage, slip-ring and panel box were all inside of a second woven galvanized cage 28 inches by 26 inches by 28 inches with a door 15 inches by 25 inches (Cage II).

A 200 watt white light was located on the exterior of Cage II. Mounted upon the wooden frame outside of Cage I and inside of Cage II on the right side near the floor of the cages were the pilot lights.

Located approximately three inches from the rear of Cage I was a red, 40 watt bulb which simultaneously lit when electroshock was presented. Approximately three inches from

the front of Cage I was a blue, 40 watt bulb which simultaneously accompanied presentation of a banana flavored food pellet. Located two inches from the right side and two inches from the bottom of Cage I was a trough into which the monkey pellet was released.

Attached to the top of Cage II was a trough containing the supply of monkey pellets. When the control switch was turned on, a solinoid switch released one pellet which traversed a polyethylene tube to the feeder trough inside of Cage I.

Aversive stimulation was delivered by an S-4 Grass stimulator with a stimulus isolation unit. The isolation unit of the stimulator was placed inside of Cage II, adjacent to Cage I and connection was made with lead wire #14. A square wave monophasic pulse was obtained. An oscilloscope was utilized to monitor the wave form.

Cage II rested upon a marble topped cabinet. Adjacent to the cabinet and separated by a four by six foot piece of one-half inch plywood was the electroencephalograph and stimulator. In the plywood was an 18 inch by 18 inch window of one-way mirror adjusted to the height of the recording cage for viewing the subject.

The recording room was eight feet by sixteen feet by nine feet with one covered window and one door. There was an exhaust ventilator fan in the ceiling which presented white noise. All ceiling lights were turned off and the door closed during each recording session.

Procedure

Electroencephalographic recordings were made 50 minutes per day for a total of 88 recordings, or until death, for a period of five months. The subjects were not restrained. The order of subjects for daily recordings was random and the time of day was random. The total of 88 recordings was divided into four periods: (1) After electrode implantation and prior to lesions, (2) After lesions, (3) During operant conditioning, and (4) In extinction.

Recordings began seven days after electrode implantation. Lesions were effected 38 days after electrode implantation. Recordings began three days after the lesion surgery. Ninety-five days after electrode implantation, operant conditioning ensued for 30 days and consisted of 18 sessions. Recordings continued for another 45 calendar days to achieve the 88 recordings.

Seizures were defined as high amplitude spike activity (500 uV) of a moderately high frequency (3-5 spikes/400 uSec.), domes and mittens. The researcher simultaneously monitored the EEG recording, observed the subject, and presented the reinforcement and shock manually.

Punishment consisted of electro stimulation of all seizure activity as displayed on the electroencephalogram as defined above. Electrical stimulation of the ventral posterior nucleus of the thalamus consisted of 4.4 volts with a frequency of .5, delay in milliseconds of 1.6,

duration of .3 and was presented for a variable interval averaging 8 seconds after a seizure began. Reinforcement of desirable behavior (not experiencing seizures) consisted of presentation of food pellets upon a variable interval of ten per 50 minutes, contingent upon no seizure activity for five minutes.

After the above parameters were determined, the experiment began. Subjects were randomly assigned to the various treatments. Following are the treatments:

Treatment I. The subject assigned to this treatment is referred to as Subject 1, Control. This subject was not subjected to experimental manipulations. Only electrodes were implanted. No lesions were effected. Recordings were taken. This subject served as the control.

Treatment II. The one subject assigned to this treatment is referred to as Subject 2, Alumina Cream Lesion, Control for Conditioning. This subject was implanted with electrodes, lesioned with alumina cream, but received no operant conditioning. Recordings were taken. This subject served as a control for conditioning.

Treatment III. The one subject assigned to this treatment is referred to as Subject 3, Alumina Cream Lesion, Conditioned. This subject was implanted with electrodes, was lesioned with alumina cream, and received operant conditioning. Recordings were taken.

Treatment IV. The one subject assigned to this treatment is referred to as Subject 4, Blunt Dissection,

Control for Conditioning. This subject was implanted with electrodes, was lesioned with a blunt dissection, received no operant conditioning, and was recorded until the animal became deceased.

Treatment V. The one subject assigned to this treatment is referred to as Subject 5, Blunt Dissection, Conditioned. This subject was implanted with electrodes, was lesioned with a blunt dissection, received operant conditioning, and was recorded until the animal became deceased.

Histology. Rather than verify electrode placement, histology was utilized to check for neural degeneration and muscle atrophy of the heart. Upon demise, the brains and hearts were removed and stored in 10% formalin solution until sections were made. Subjects which were sacrified were anesthetized and the thoracic cavity entered. With the lungs collapsed and the heart still beating, 10% formalin solution was injected into the left ventricle of the heart to circulate to the brain. The brain and heart were removed and stored in 10% formalin solution until sections were made.

CHAPTER III

RESULTS

Subject 1, Control; Subject 2, Alumina Cream, Control for Conditioning; and Subject 3, Alumina Cream, Conditioned, were sacrificed at the end of the research. Subject 4, Blunt Dissection, Control for Conditioning, became deceased on the 69th post-operative day. Subject 5, Blunt Dissection, Conditioned, became deceased on the 103 post-operative day. All subjects developed mild epileptic seizure patterns in the EEG after electrode implantation (See Figure 1). The seizure patterns diminished with Subject 1. After creation of the alumina cream lesions in Subjects 2 and 3, the seizures became severe within 12 days. Seizures remained severe with Subject 2. After conditioning, the seizures decreased in number and severity for Subject 3. After blunt dissection, seizures continued to increase in severity with Subject 4 until death occurred. After blunt dissection with Subject 5, seizures increased. This subject received conditioning and the number of seizures were decreasing when death occurred.

Subject 1, Control. From the seventh through the 37th day after electrode implantation, seizure activity in the right frontal and right parietal areas surpassed other areas. After the 38th day, seizure activity equalized in all areas. By the 70th day after electrode implantation, the seizures began to decrease. During the first 37 days, this subject was irritable, i.e., he was difficult to handle,

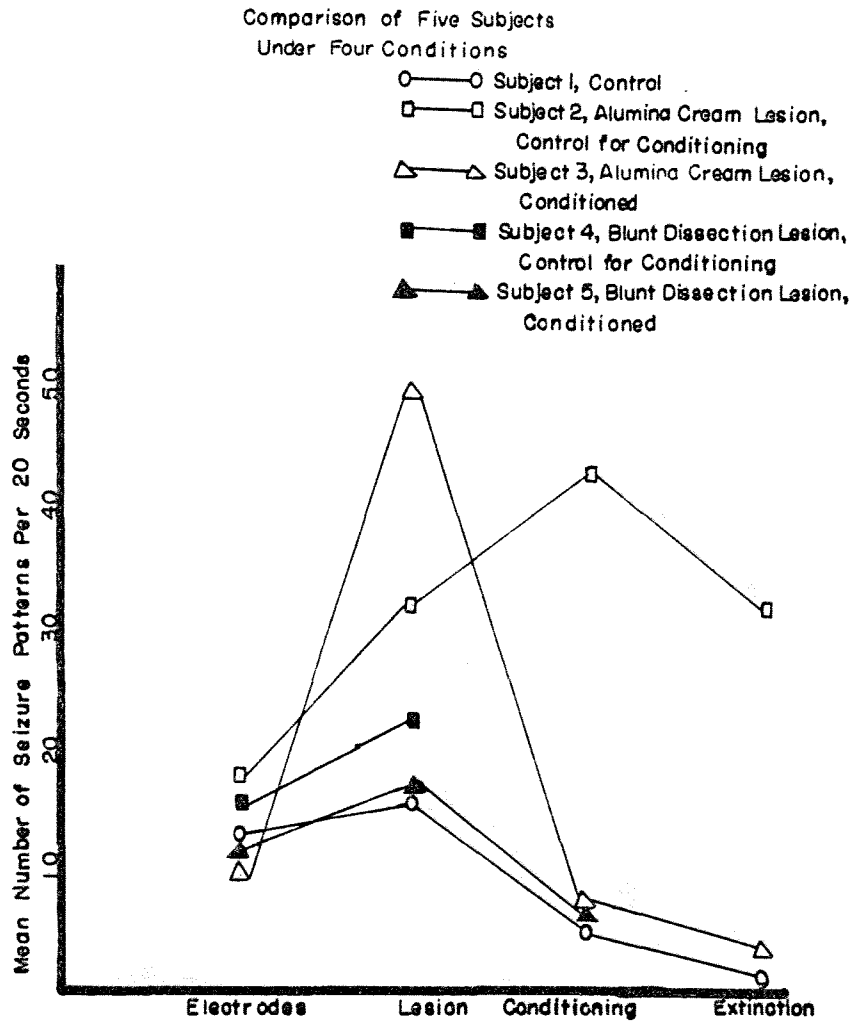


Figure 1. Mean number of seizures per subject as a function of four conditions.

growled, and bit. During EEG seizure activity, the subject displayed hyperactive behavior. He paced the recording cage and attempted to climb the sides of the cage. After the 38th day, the subject most frequently crouched in the center of the cage and slept (See Figures 2 and 3).

Subject 2, Alumina Cream Lesion, Control for Conditioning. Prior to the implantation of electrodes, this subject would not approach the experimenter or attempt to escape. He was easy to handle. After electrode implantation, the subject's behavior both in his home cage and in the recording cage remained unchanged. After the 38th day when alumina cream was injected into the nodosa ganglia, both the EEG and behavior were indicative of seizures. When seizures were observed on the EEG, the subject simultaneously salivated, defecated, displayed clonic, tonic behavior and became difficult to handle. The mean number of spikes for all electrodes increased from 17.55 to 31.96 after effecting the lesion. After the 95th day, the mean number of spikes increased to 42.90 and the last 45 days of the research, decreased to 31.26. The mean number of spikes for the solitary nucleus after electrode implantation was 7.21; after lesioning, 39.31; after the 95th day, 63.97 and 44.32 for the last 45 days (See Figures 4 and 5).

Subject 3, Alumina Cream, Conditioned. Prior to the implantation of electrodes and lesions, this subject would jump at the side of the cage whenever anyone approached

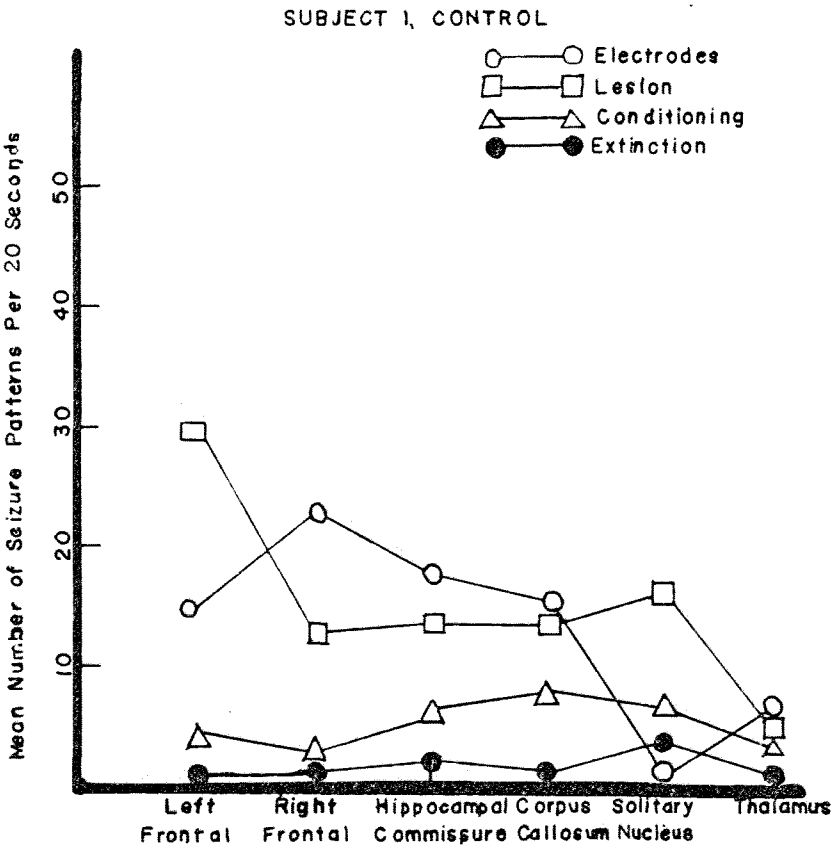
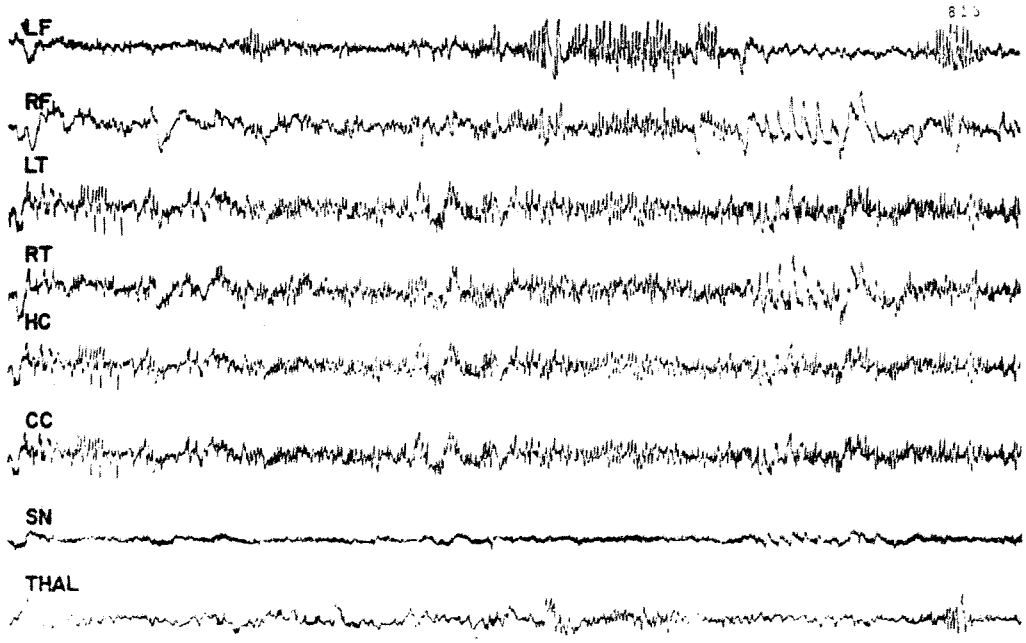
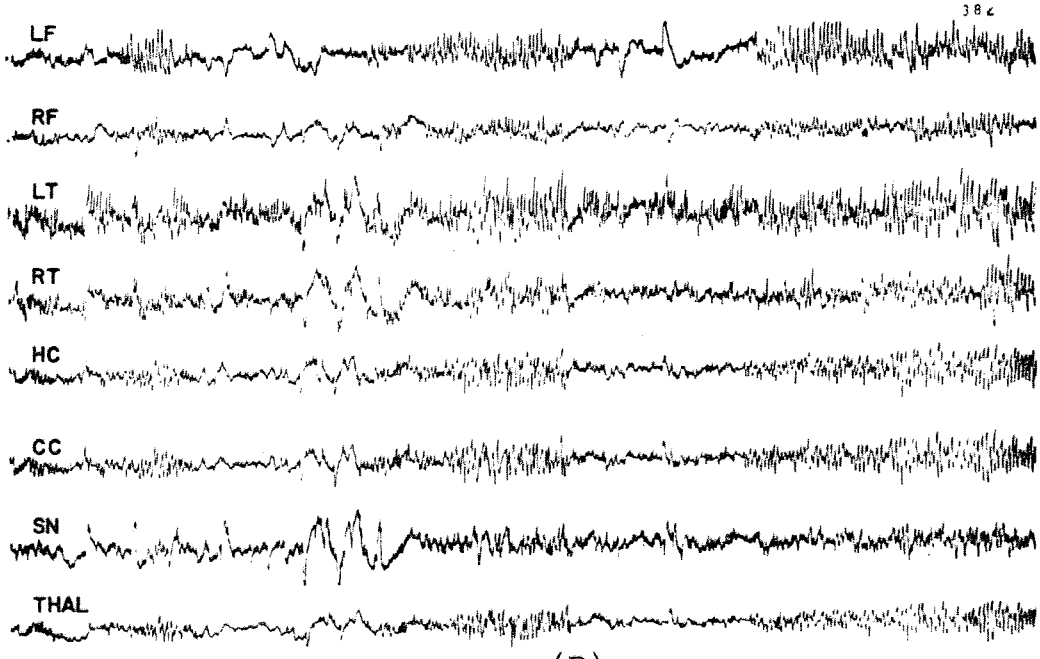


Figure 2. Mean number of seizures for Subject 1, Control, at six electrodes as a function of four conditions.



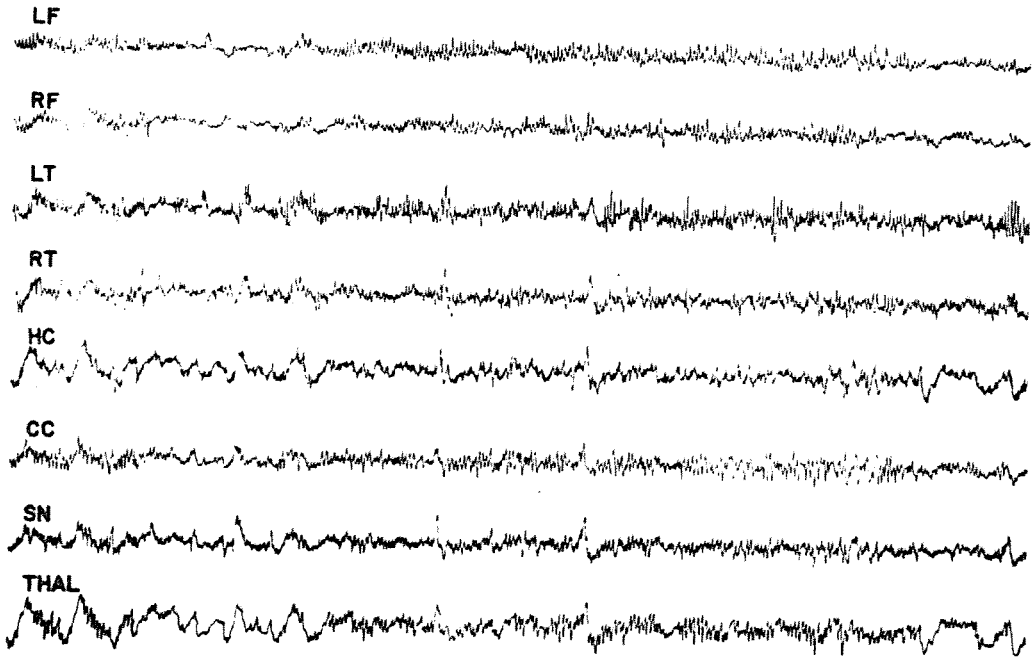
(A)



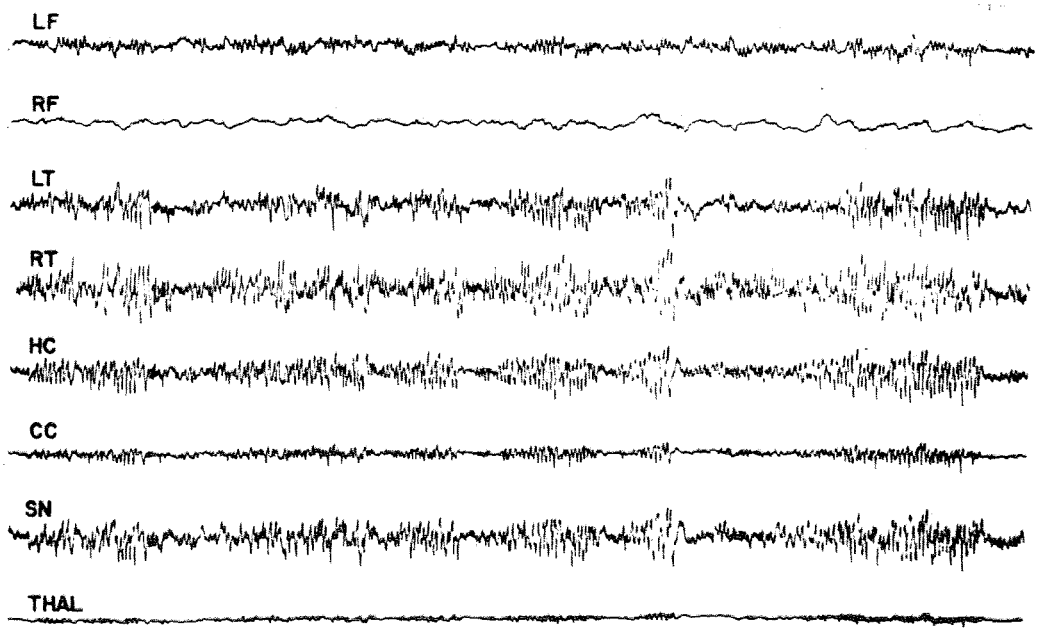
(B)

Figure 3. Samples of EEG recordings for Subject 1, Control, for four conditions: (A) Electrode implantation; (B) Lesion; (C) Conditioning; and (D) Extinction.

Figure 3 (Continued)



(C)



(D)

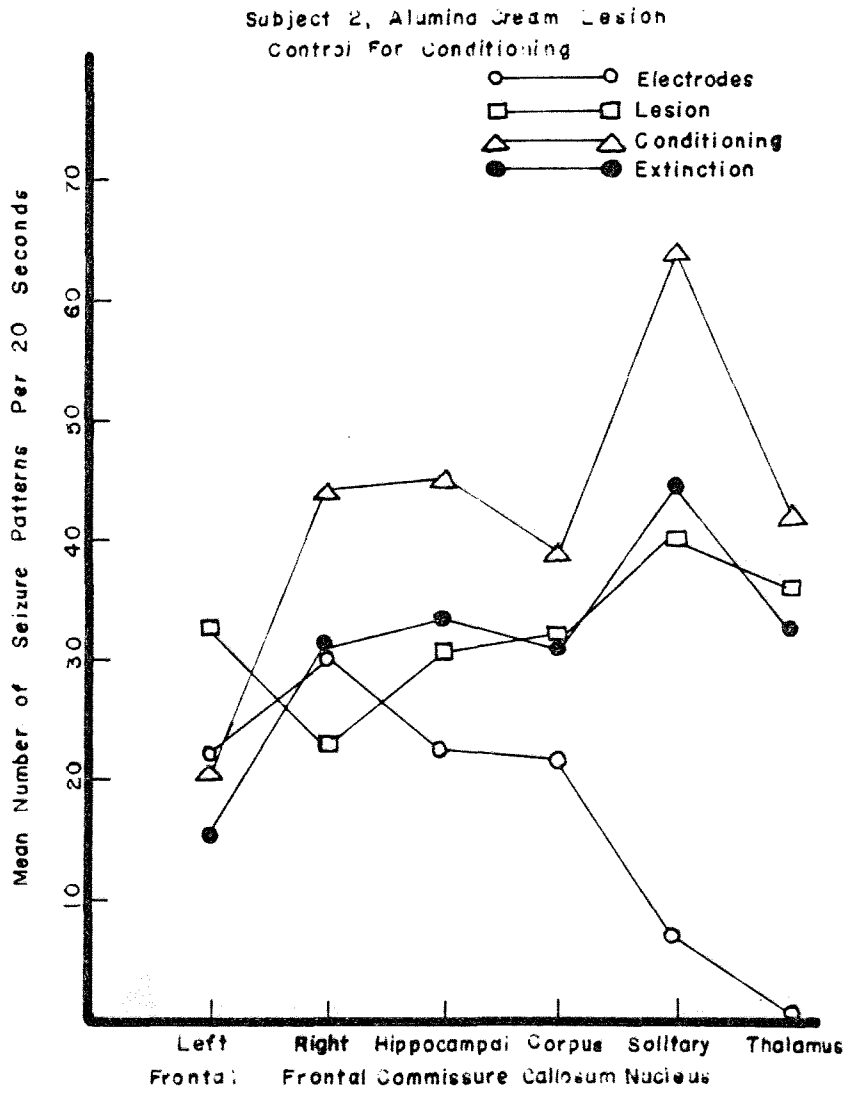
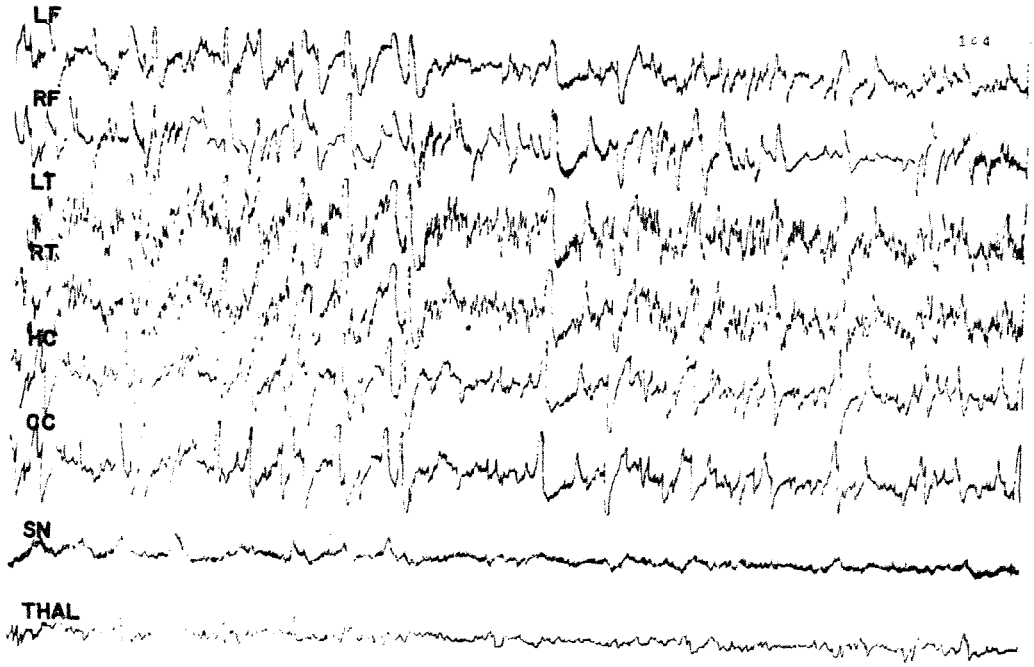
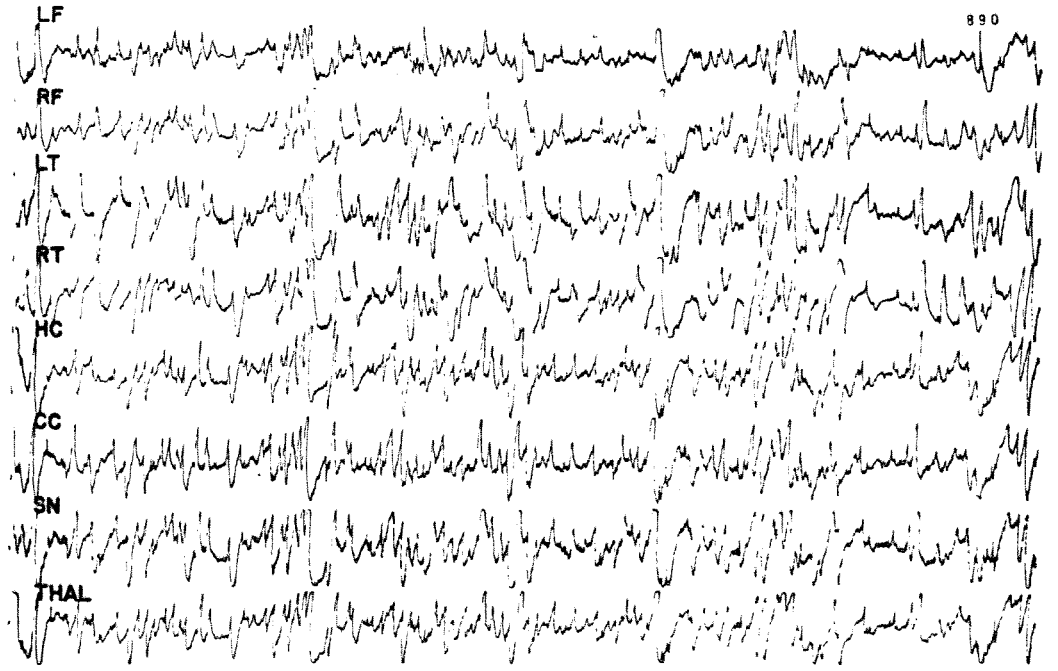


Figure 4. Mean number of seizures for Subject 2, Alumina Cream, Control for Conditioning, at six electrodes as a function of four conditions.



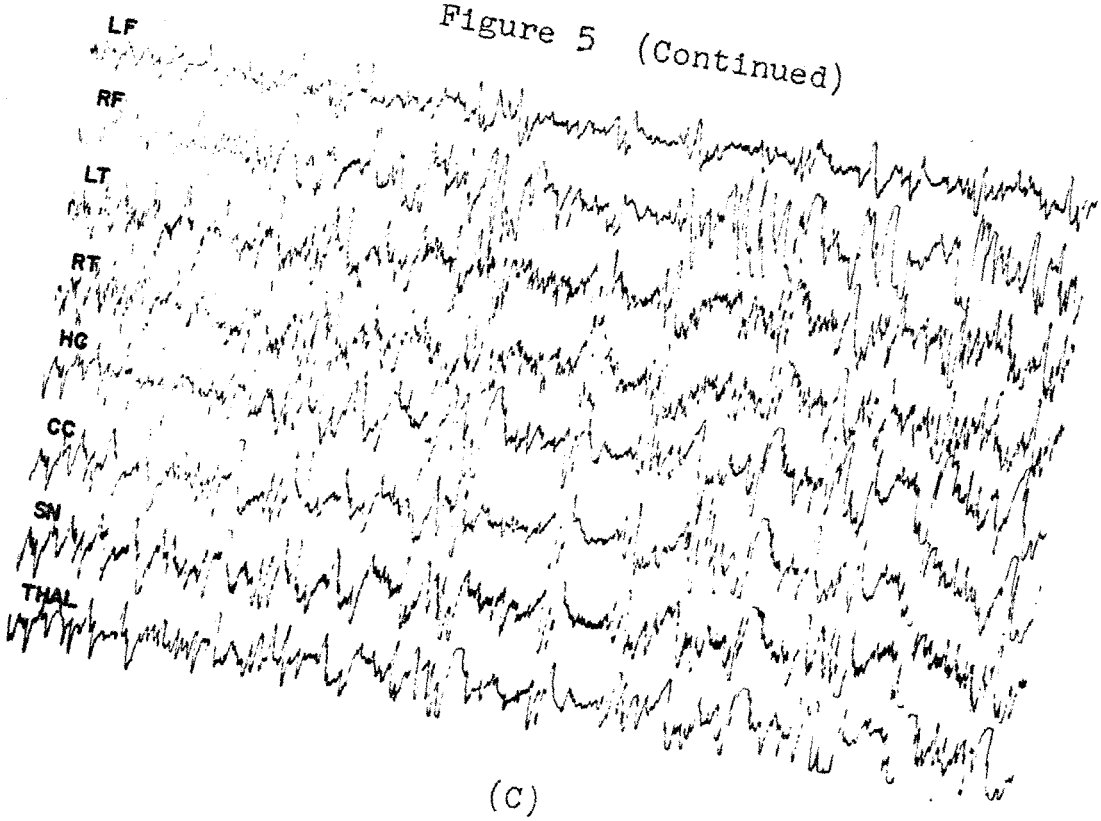
(A)



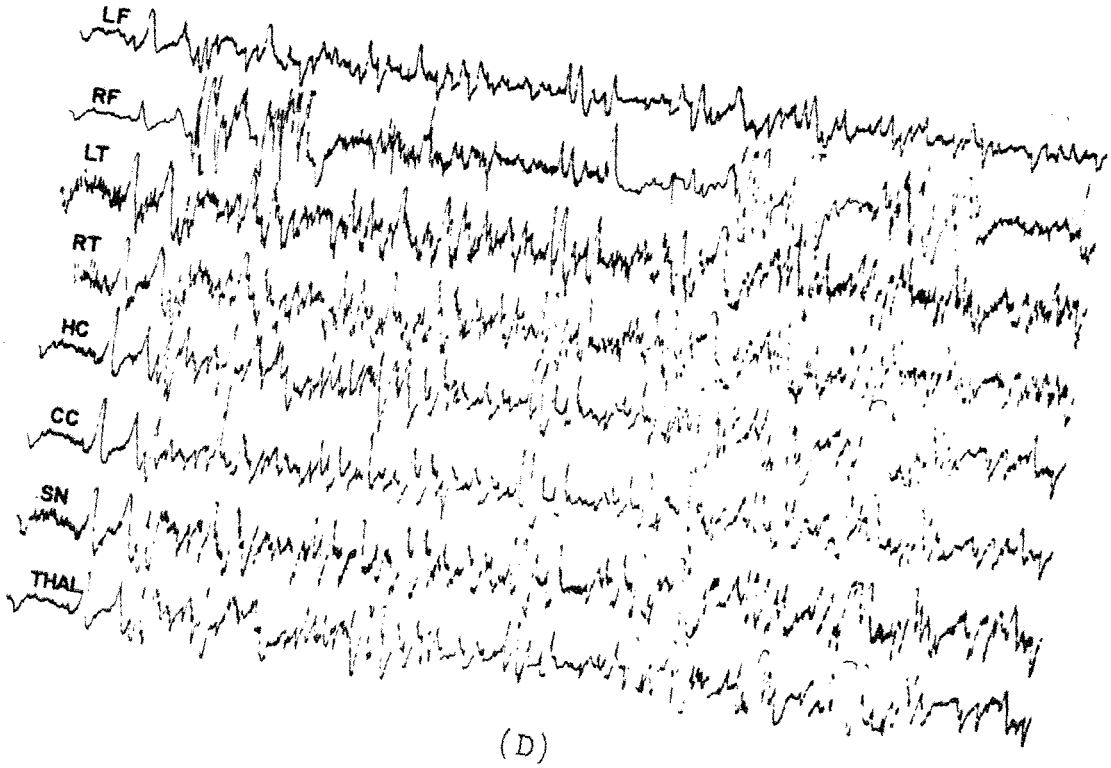
(B)

Figure 5. Samples of EEG recordings for Subject 2, Alumina Cream, Control for Conditioning, for four conditions: (A) Electrode implantation; (B) Lesion; (C) Conditioning; and (D) Extinction.

Figure 5 (Continued)



(C)



(D)

and was difficult to handle. After effecting the alumina cream lesion, the mean number of spikes for all electrodes increased from 9.53 to 49.93. During conditioning, the mean number of spikes decreased to 6.71. During extinction, the spikes first increased and then decreased to a mean of 3.27. At the height of seizure activity after effecting the lesion, this subject would crouch near and facing the door of the recording cage. He would attempt to sleep when suddenly he would be thrown backwards against the side of the cage. If the subject was sitting up, the seizure would begin as a twitch in the right foot and move up the right side of the body and then to the left side of the body and extremities, indicative of a Jacksonian seizure. During such behavior, the subject would salivate, twitch, and defecate. After such episodes, the subject displayed complete exhaustion and would either hang on the woven wire of the cage or lie down panting. After conditioning, the subject would usually crouch and sleep within five minutes of entering the recording cage. He was not only easy to handle but appeared to enjoy it. Prior to creation of the lesion, seizure activity for the solitary nucleus and thalamus were lower than the other electrodes. After effecting the lesion, the solitary nucleus increased from a mean of 4.95 to a mean of 63.52. During conditioning, the mean was 10.44 and decreased to a mean of 3.99 (See Figures 6, 7, 8, 9, 10, 11, and 12).

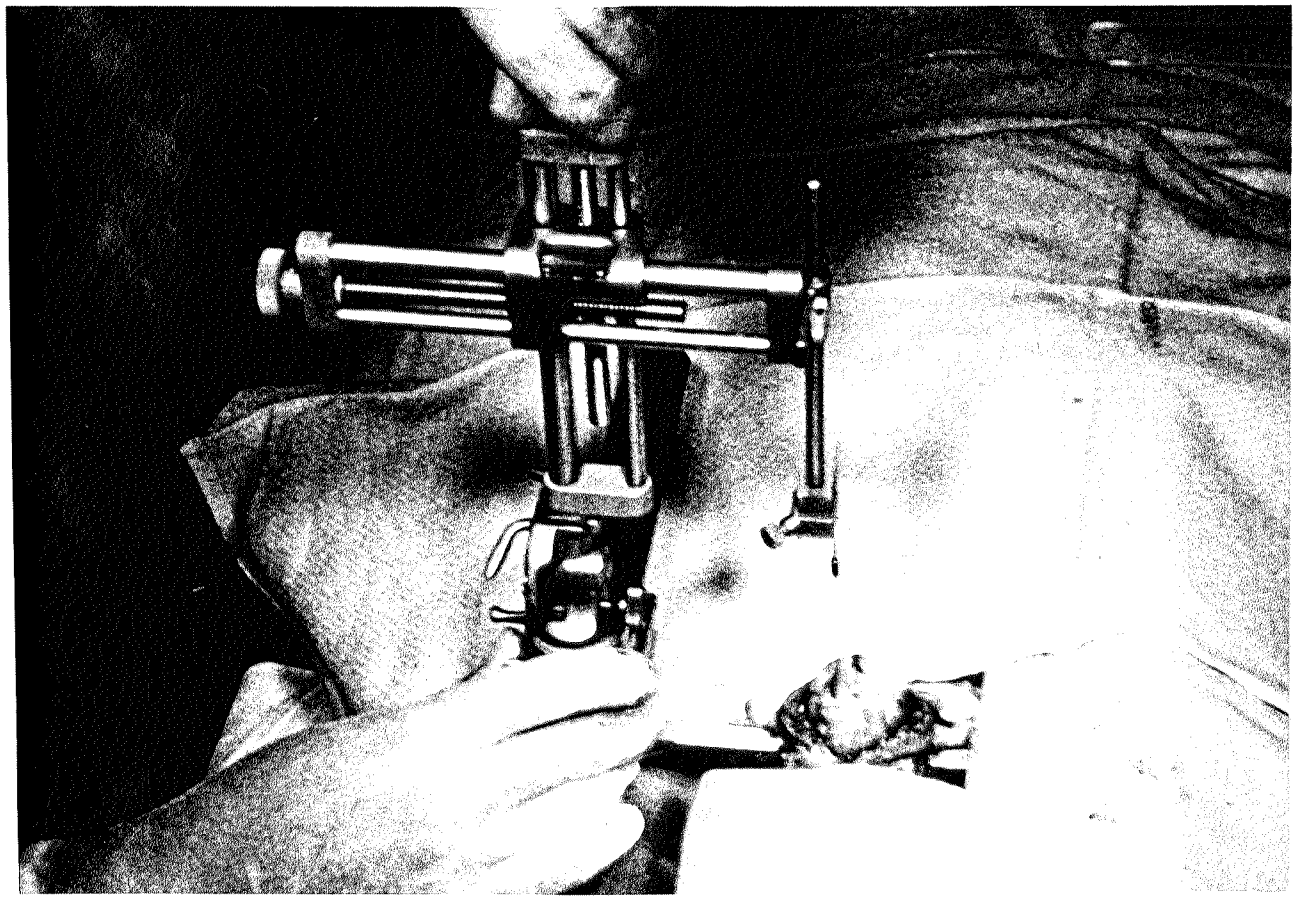


Figure 6. Surgical procedure. Electrode implantation of Subject 3, Alumina Cream, Conditioned.

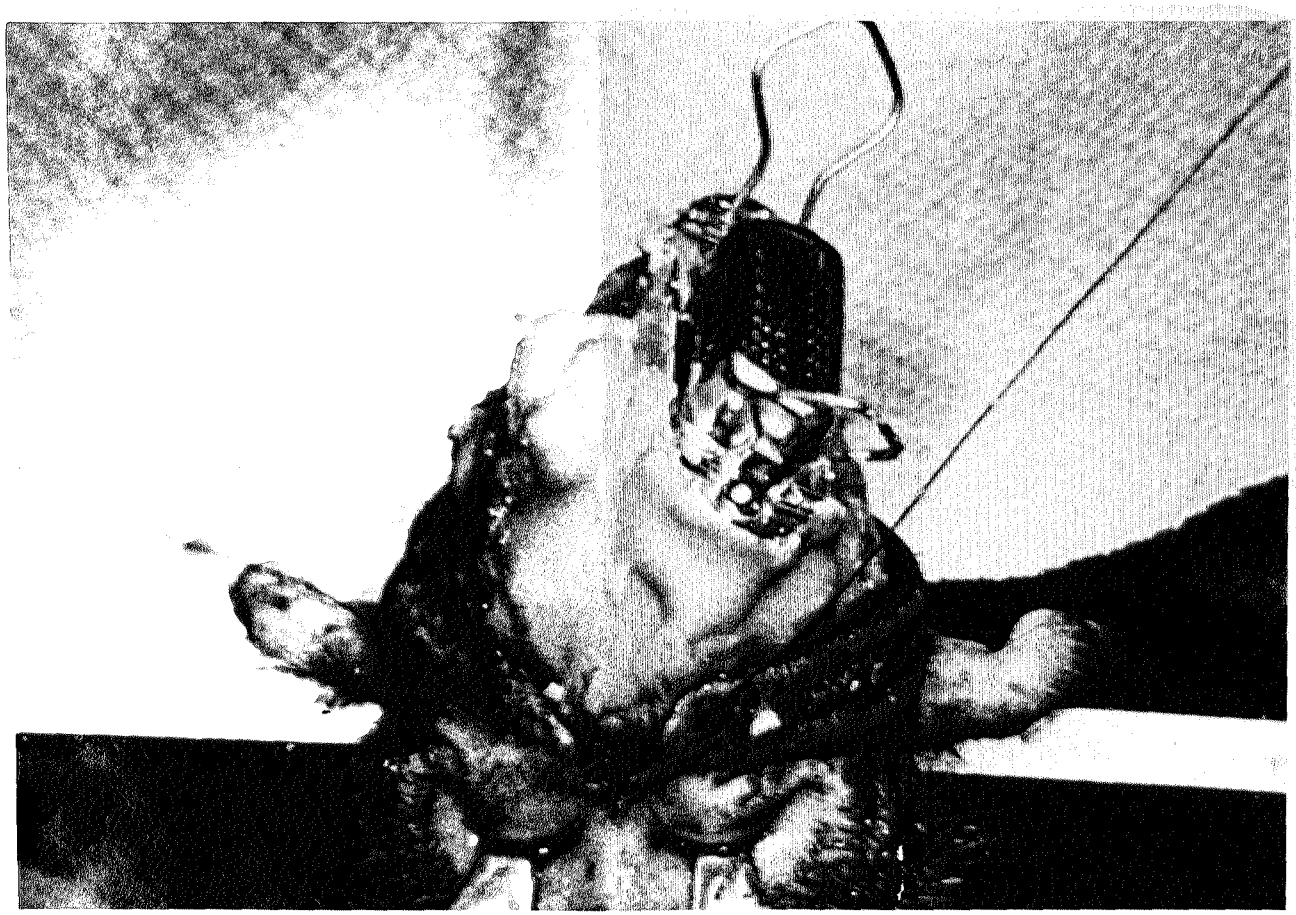


Figure 7. Completion of surgery for Subject 3, Alumina Cream, Conditioned.

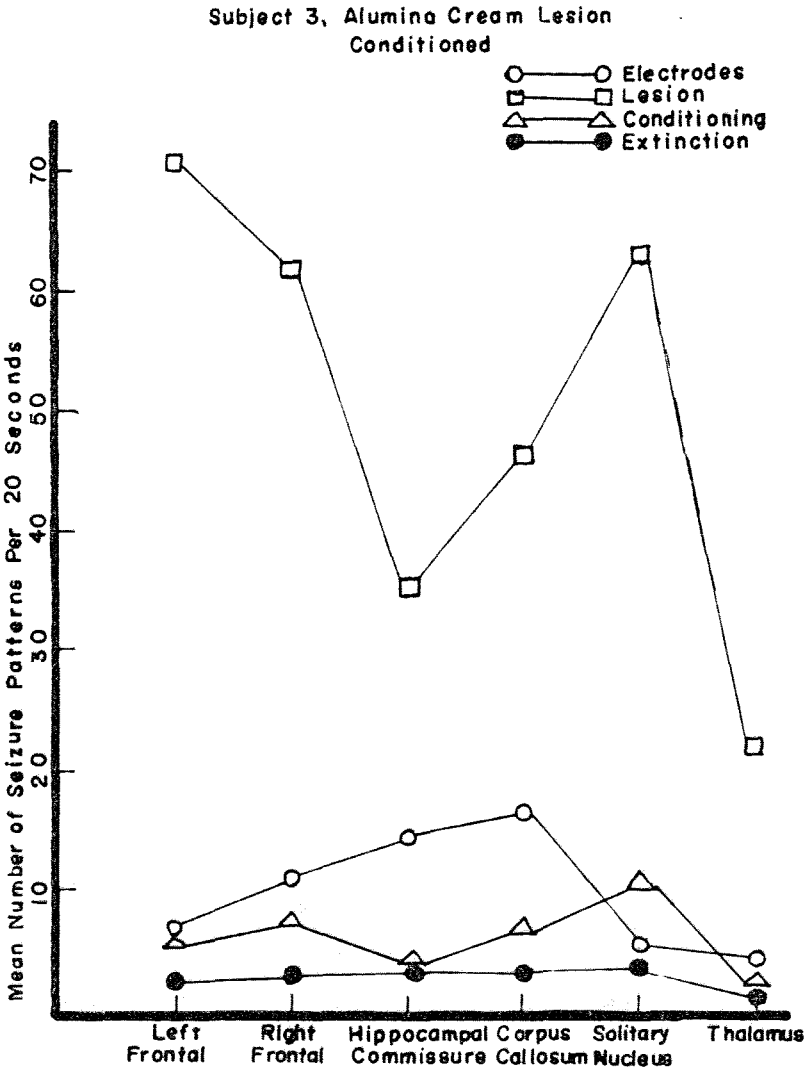
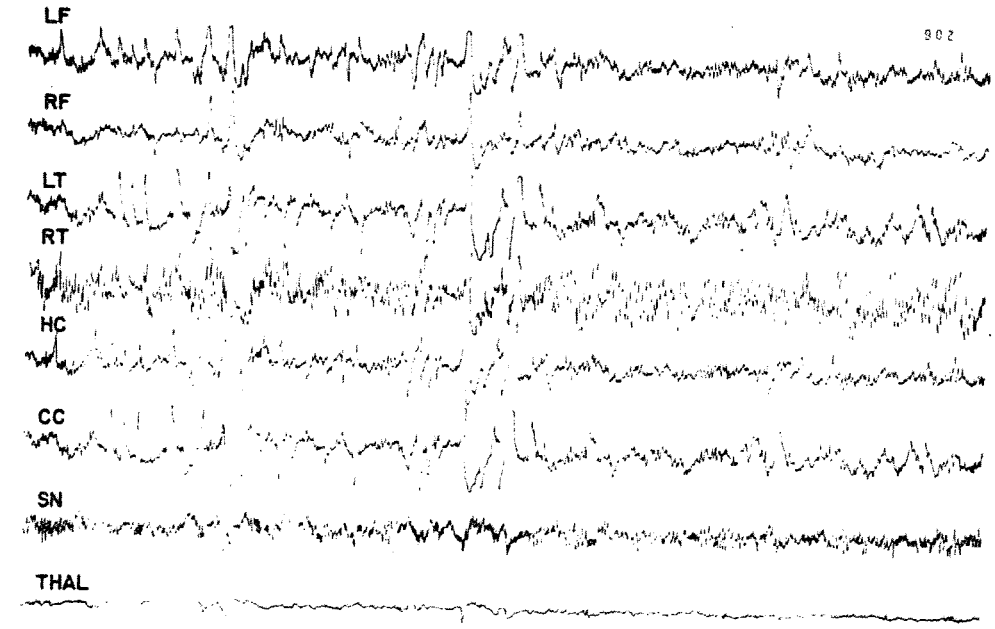
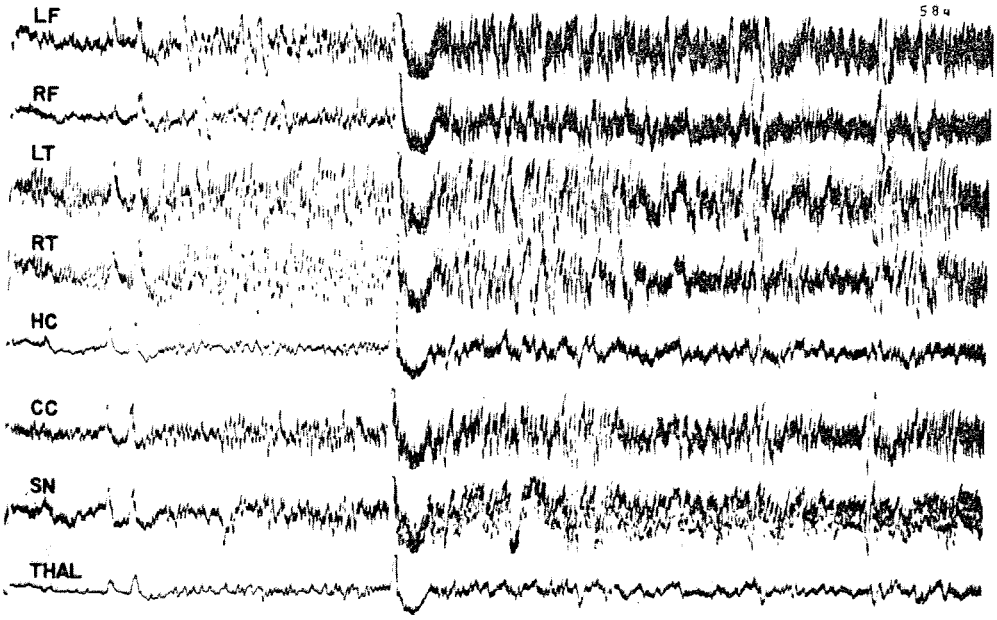


Figure 8. Mean number of seizures for Subject 3, Alumina Cream, Conditioned, at six electrodes as a function of four conditions.



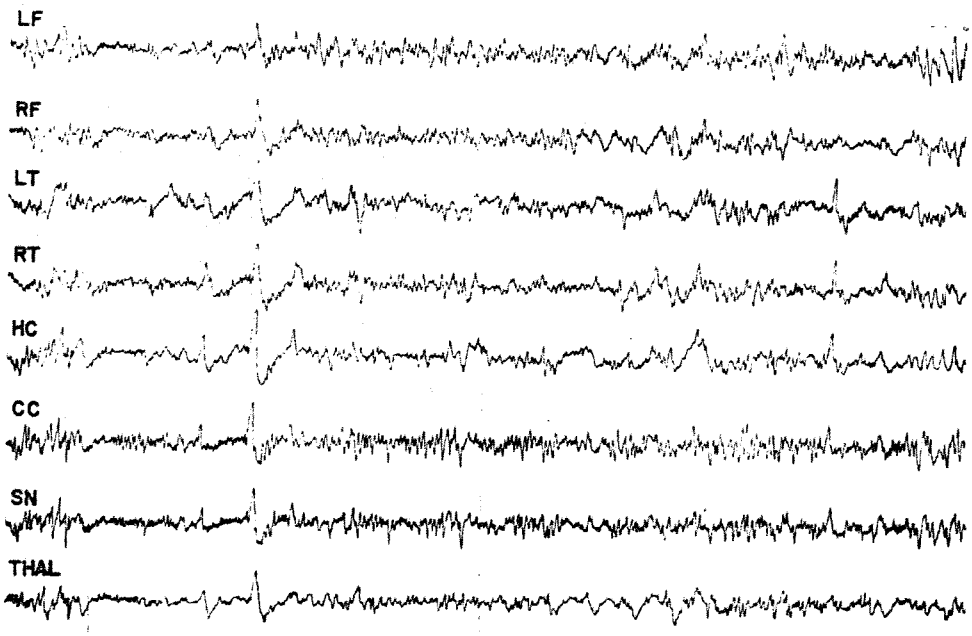
(A)



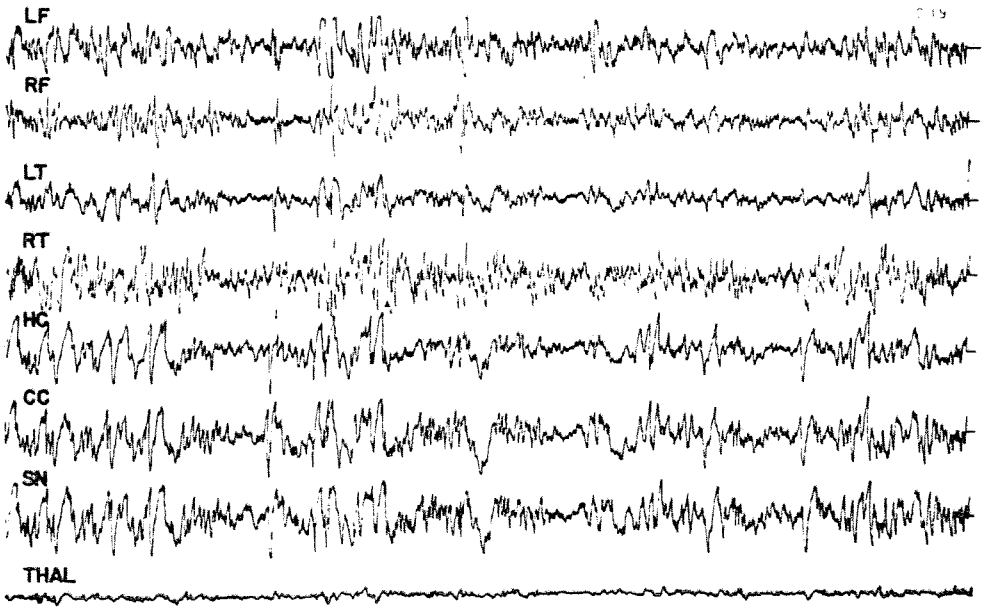
(B)

Figure 9. Samples of EEG recordings for Subject 3, Alumina Cream, Conditioned, for four conditions: (A) Electrode implantation; (B) Lesion; (C) Conditioning; and (D) Extinction.

Figure 9 (Continued)



(C)



(D)

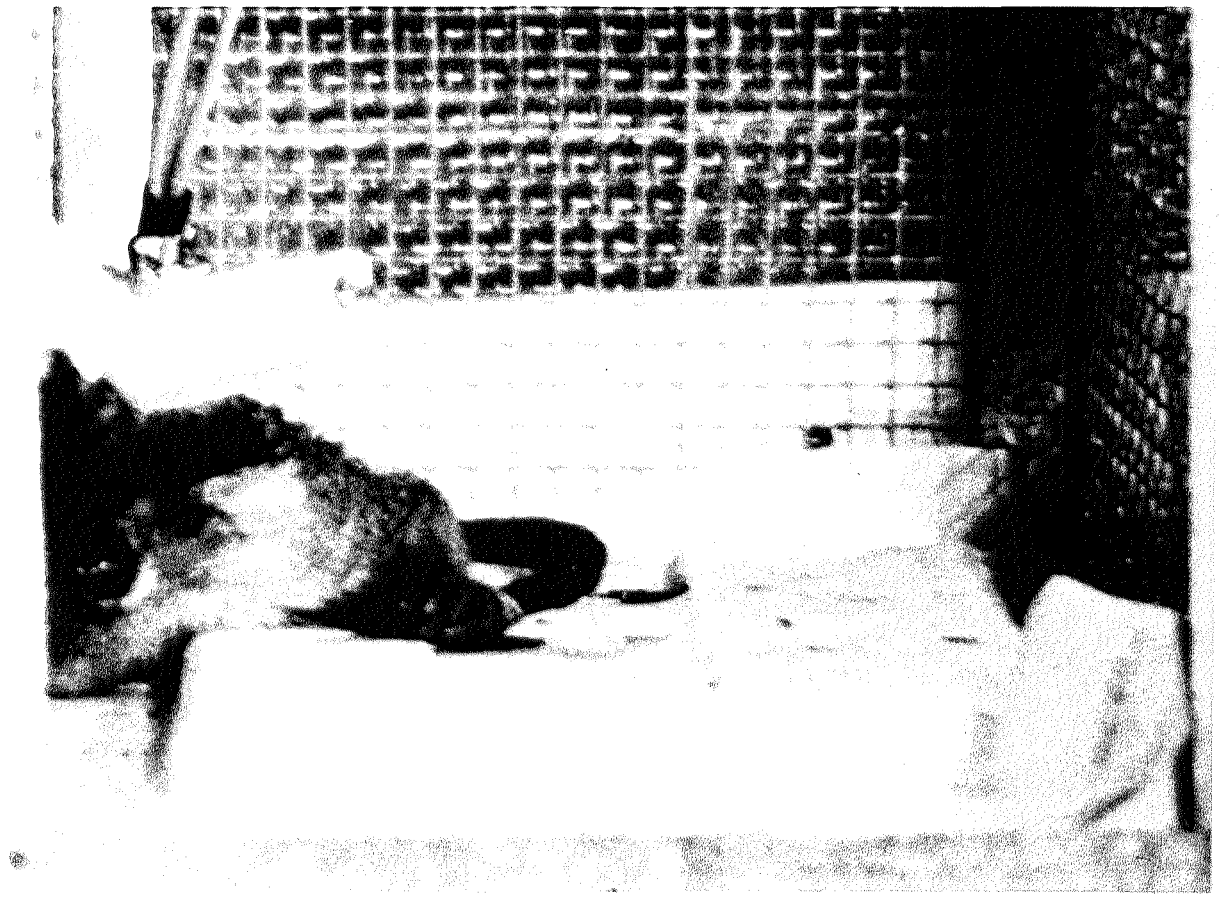


Figure 10. Subject 3, Alumina Cream, Conditioned, experiencing a seizure during EEG recording session.

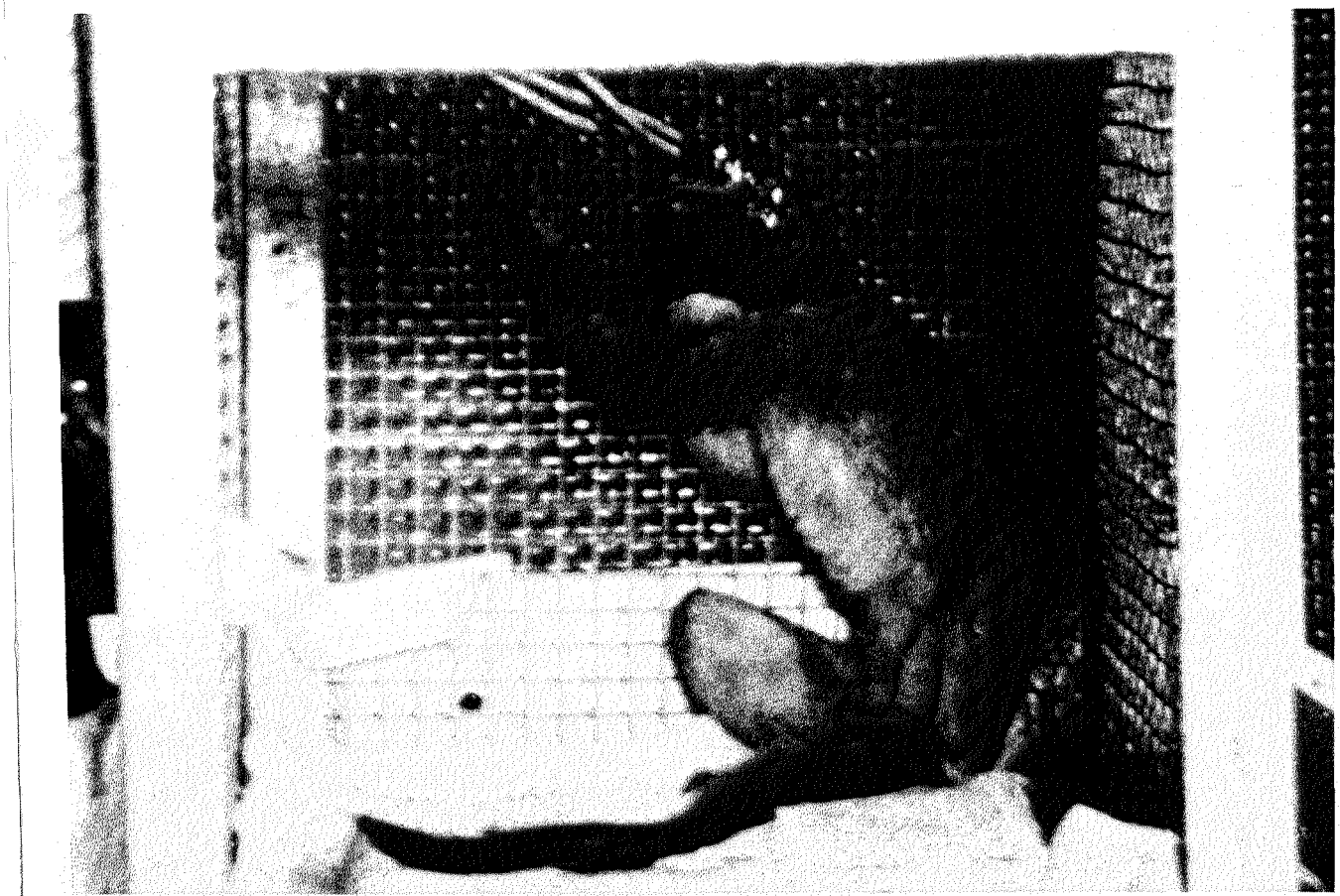


Figure 11. Subject 3, Alumina Cream, Conditioned, exhausted after seizure.

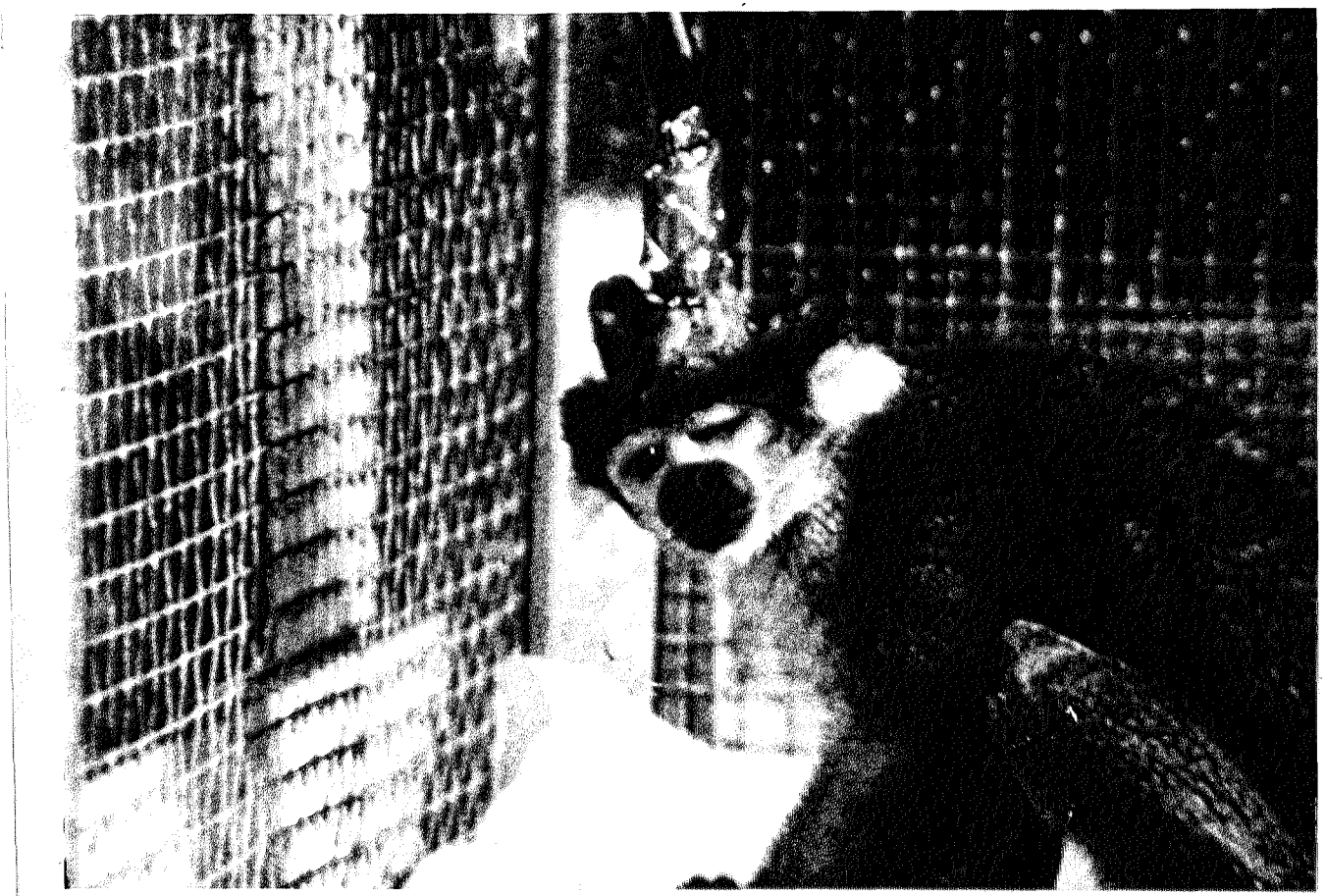


Figure 12. Subject 3, Alumina Cream, Conditioned, during Period 4 (Extinction).

Subject 4, Blunt Dissection, Control for Conditioning. After electrode implantation, the mean number of seizures for all electrodes was 16.32. The mean increased after effecting the lesion to 22.52 at the time of death. During seizures the subject would squeal, pull its body first to the right and then to the left while defecating and salivating. The eyes were diverted. The mean number of seizures for the solitary nucleus increased from 14.05 to 28.01 after effecting the lesion. This subject became deceased on the 69th post-operative day (See Figures 13 and 14).

Subject 5, Blunt Dissection, Conditioned. After the blunt dissection lesion was created, the mean number of seizures for all electrodes increased from 12.18 to 16.42 (See Figures 15 and 16). The subject would normally pace both his home cage and the recording cage. As the seizures became more severe, the subject attempted to crouch in the corner of the recording cage. As a seizure began, his body would pull either right or left and then reverse. On several occasions the subject would stand with his body rigid and be thrown backwards against the cage. This behavior was accompanied with salivating and defecating, followed by exhaustion. After conditioning commenced, both the severity and number of seizures decreased. This subject became deceased on the 103 post-operative day. The body was found in an elongated position with the head pulled back and dried emesis around the mouth.

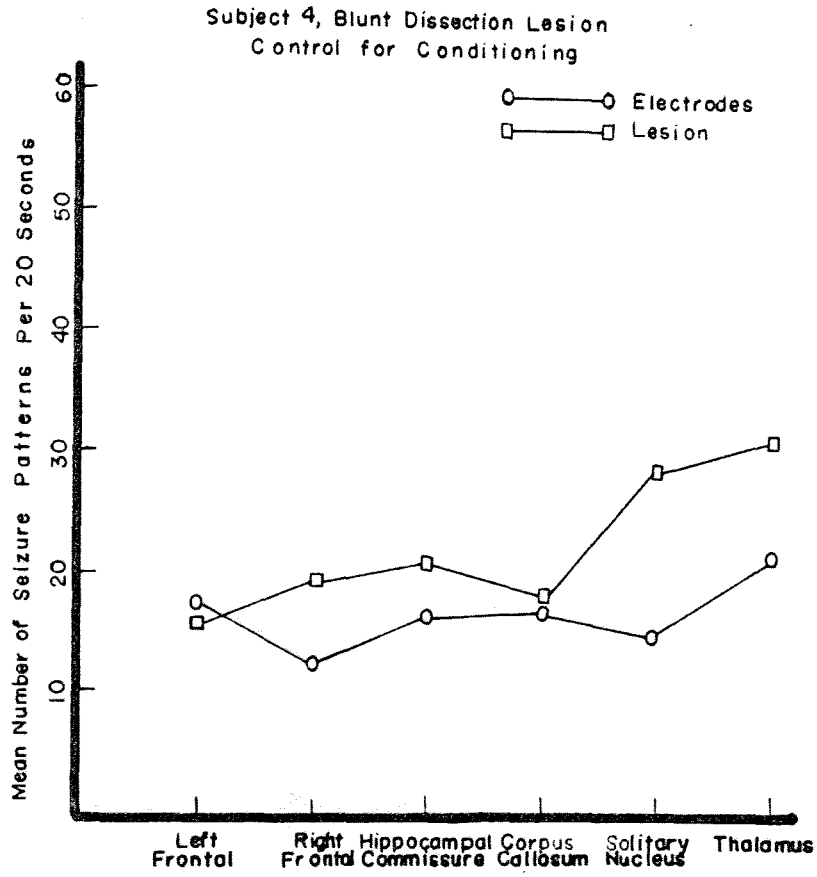


Figure 13. Mean number of seizures for Subject 4, Blunt Dissection, Control for Conditioning, at six electrodes as a function of two conditions.

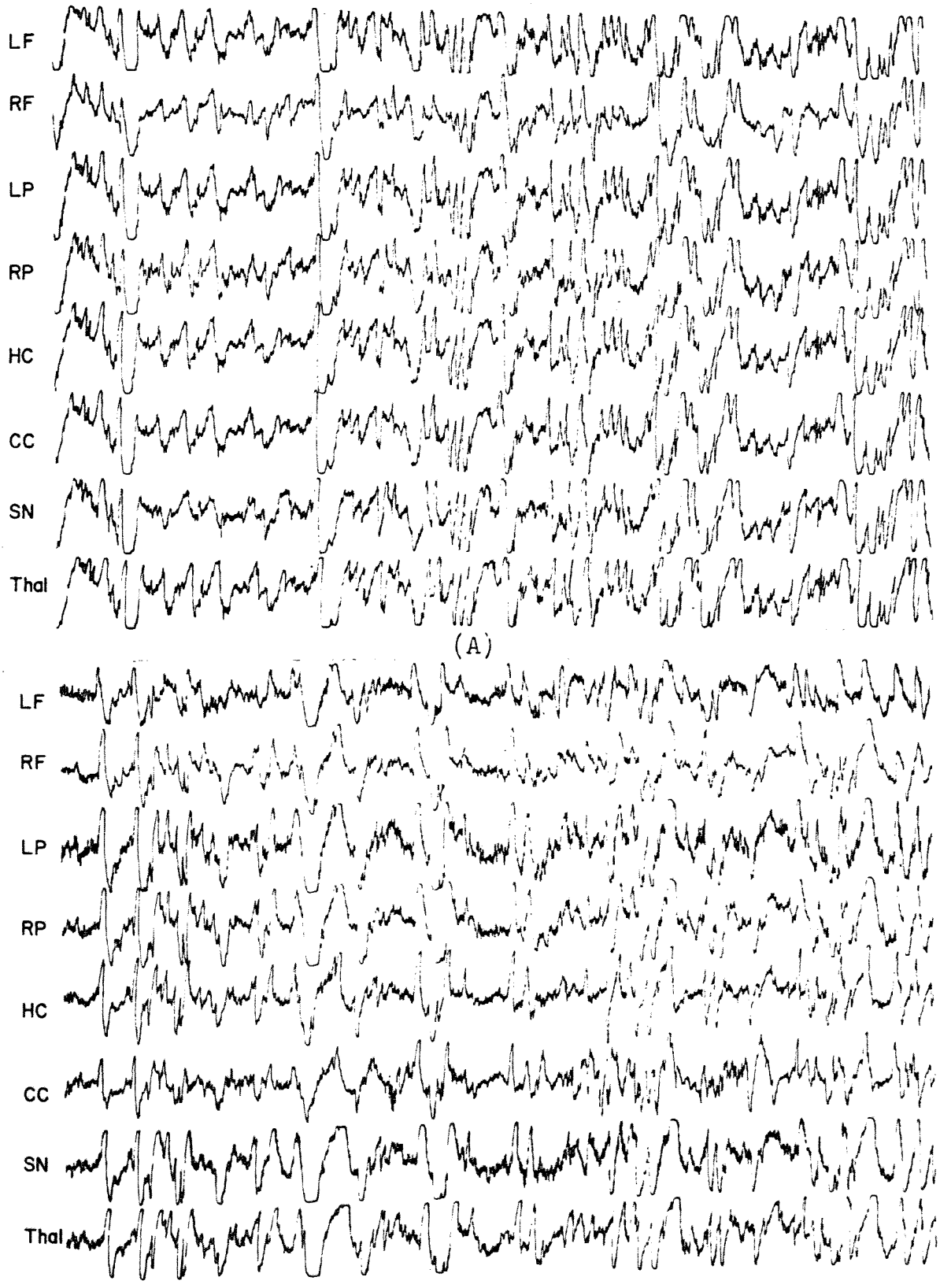


Figure 14. Samples of EEG recordings for Subject 4, Blunt Dissection, Control for Conditioning, for two conditions: (A) Electrode implantation; (B) Lesion.

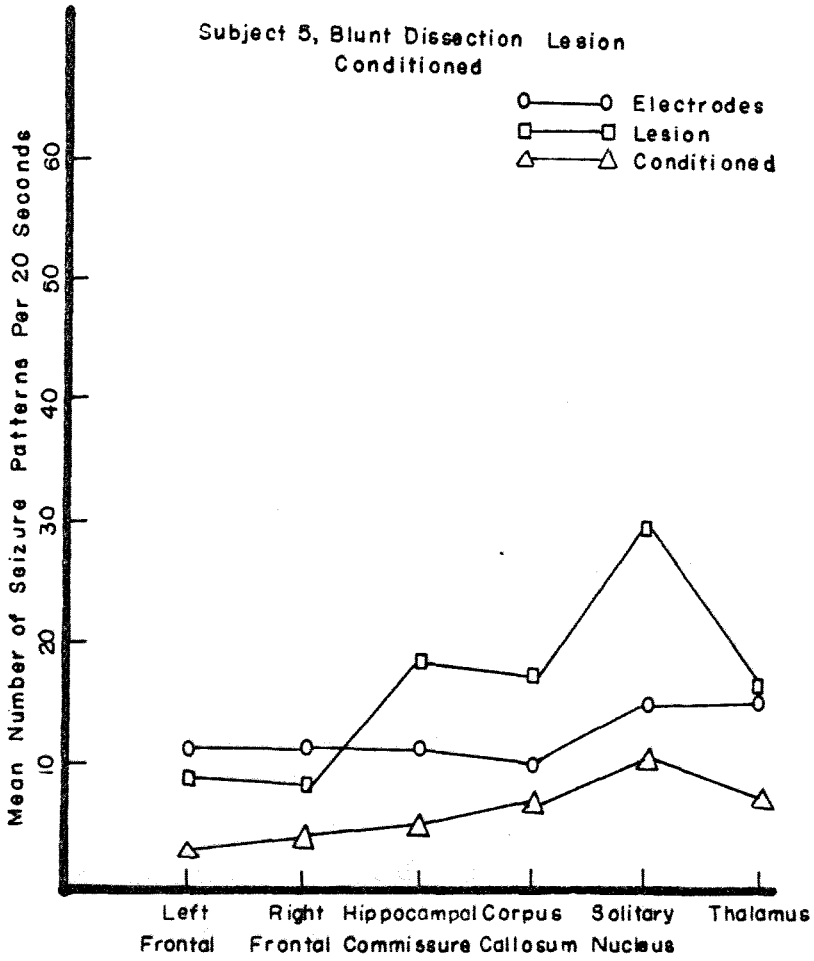


Figure 15. Mean number of seizures for Subject 5, Blunt Dissection, Conditioned, at six electrodes as a function of three conditions.

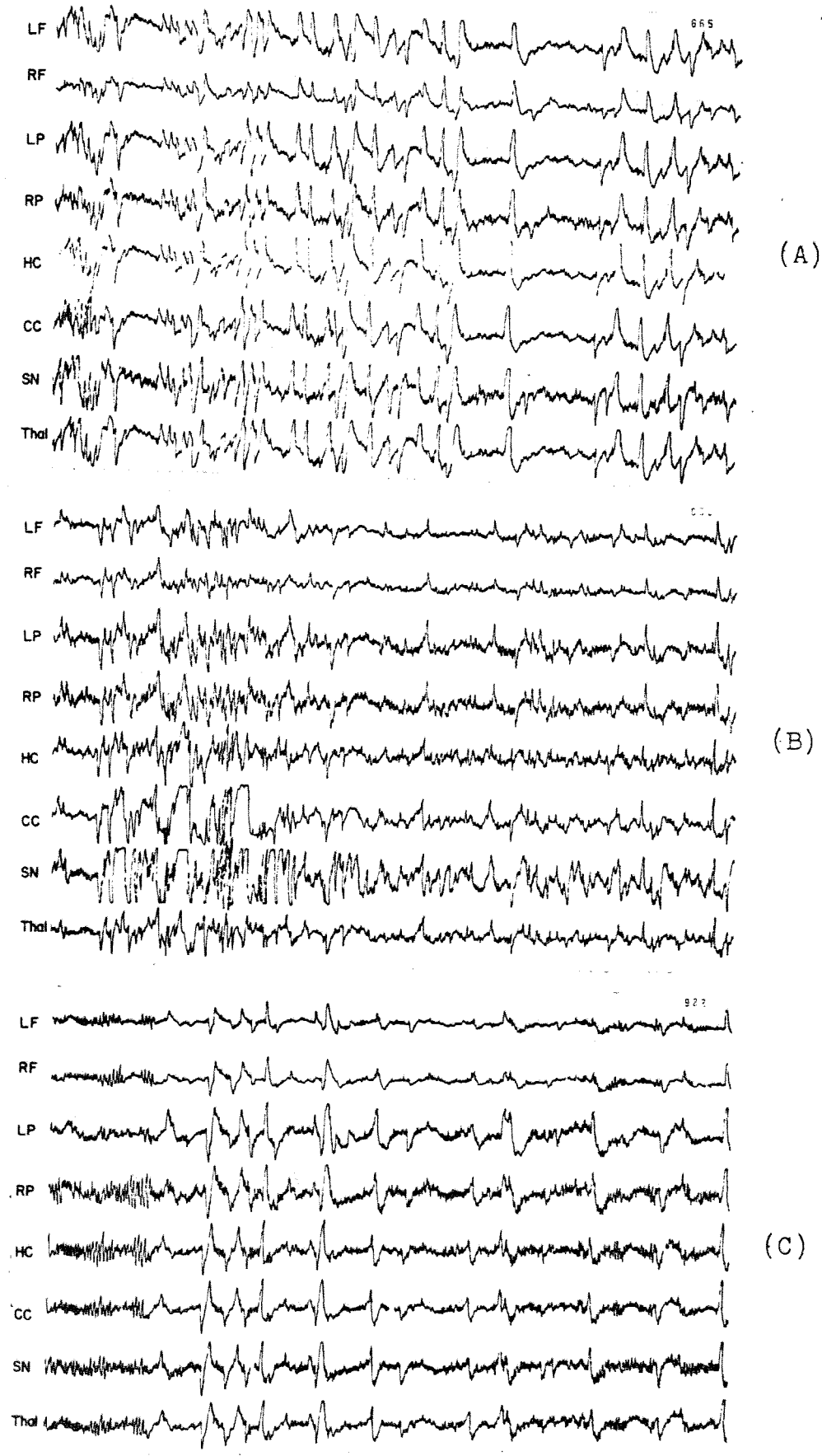


Figure 16. Samples of EEG recordings for Subject 5, Blunt Dissection, Conditioned, for three conditions: (A) Electrode implantation; (B) Lesion; and (C) Conditioning.

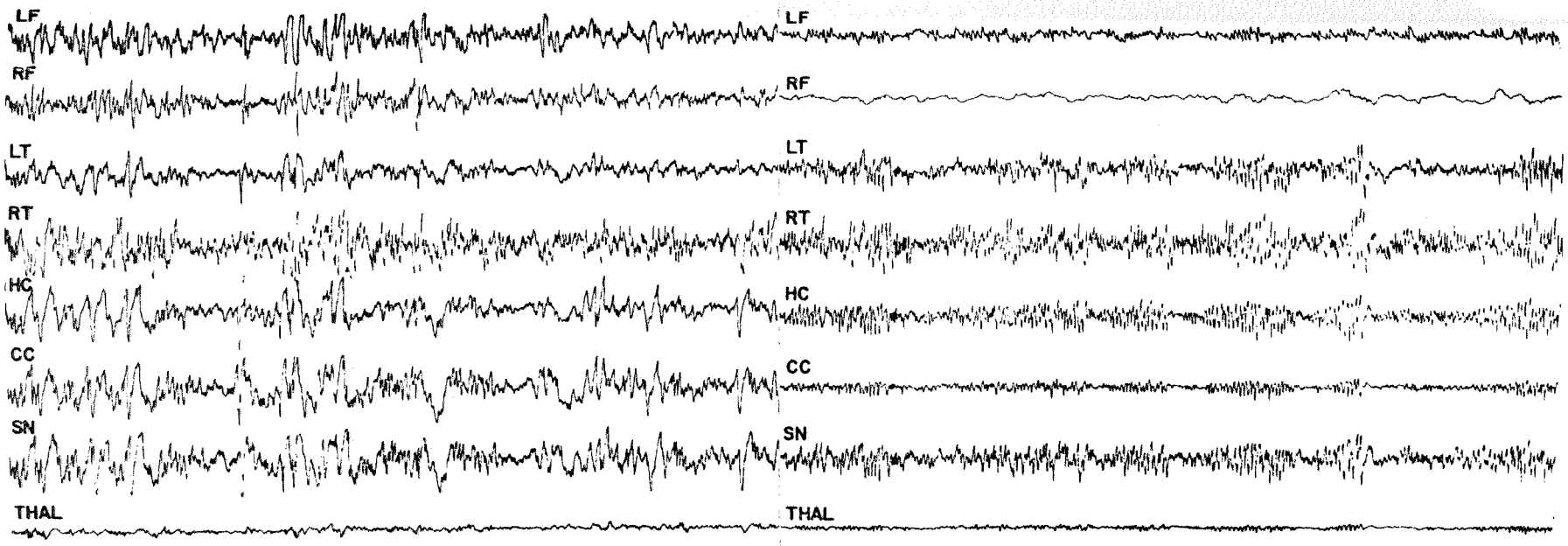
Mean seizures were computed on all subjects and are shown in Tables 3, 4, 5, 6 and 7 of the Appendix. Seizures were counted on 20 randomly selected pages on each of the last four days of the four time periods: (1) After electrode implantation, (2) After lesion, (3) After conditioning, and (4) Extinction.

An analysis of variance was computed on Subjects 1, 2, and 3, and resulted in a significant effect between the seizure activity of the various electrodes, between the four time periods, over various days within the time period for each subject and between subjects (See Table 1 of the Appendix and Figures 17, 18, 19, 20 and 21).

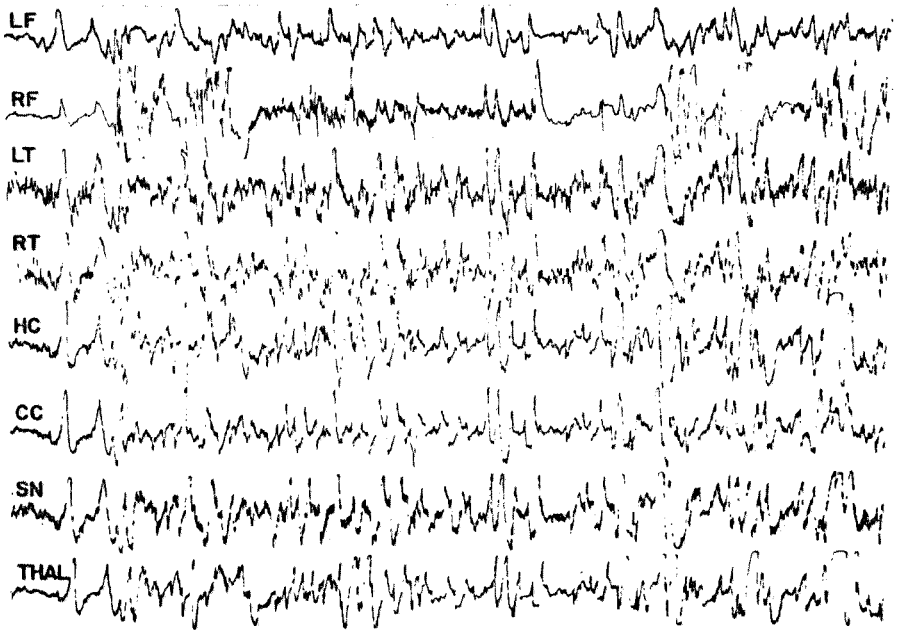
After the lesions were created in Subjects 2 and 3, there was an increase in seizure activity at the electrode placed at the solitary nucleus. As indicated in Table 1, there was also a difference in the seizure activity of the solitary nucleus between the three subjects.

Planned comparison of the means indicated there was a significant difference in the means between Subject 1 from Subjects 2 and 3. A significant difference also existed between Subjects 2 and 3 (See Table 2 and Figures 18, 19, 20 and 21).

A comparison of the treatments over the four time periods indicated significant differences between all three subjects (See Table 1). The alumina cream lesion did create seizure activity. This is reflected during the second period (See Figure 19). Both Subjects 2 and 3 displayed an



Subject 1 Subject 2



Subject 3

Figure 17. Comparison of EEG's for Subjects 1, 2, and 3 during fourth period (Extinction).

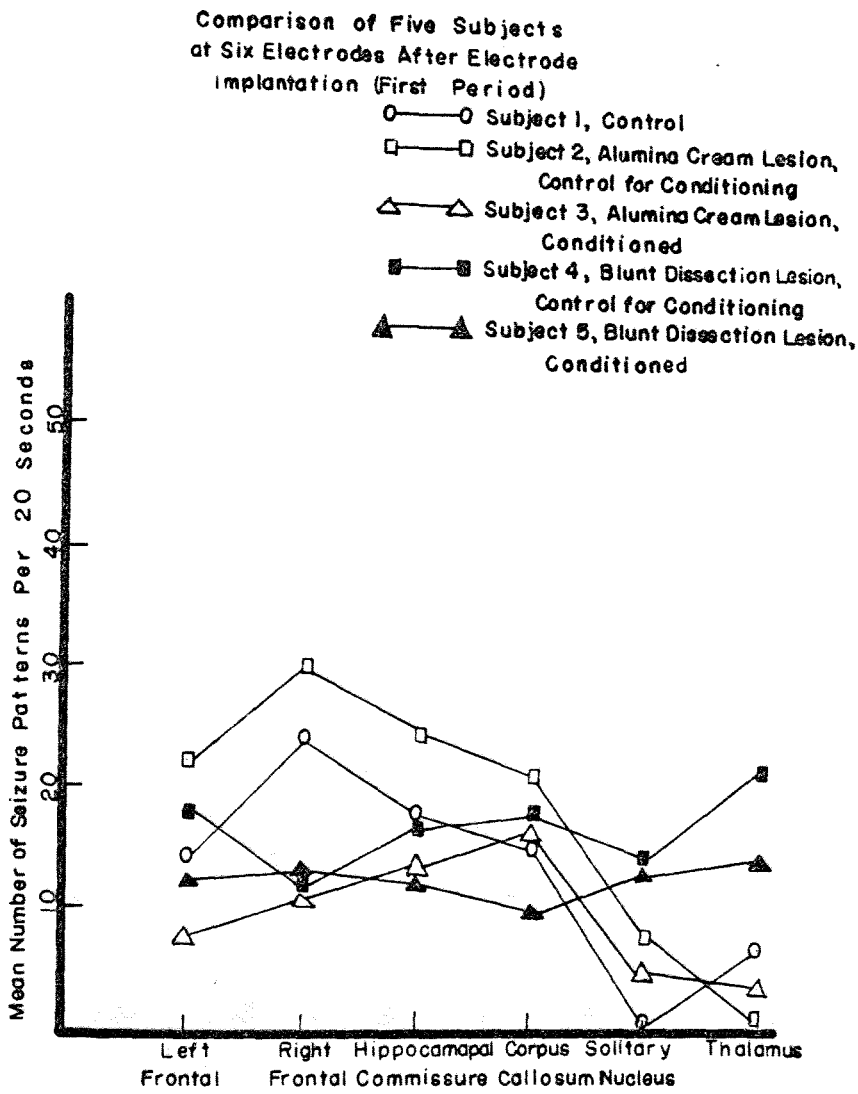


Figure 18. Mean number of seizure patterns as a function of implantation (first period) of six electrodes for five subjects.

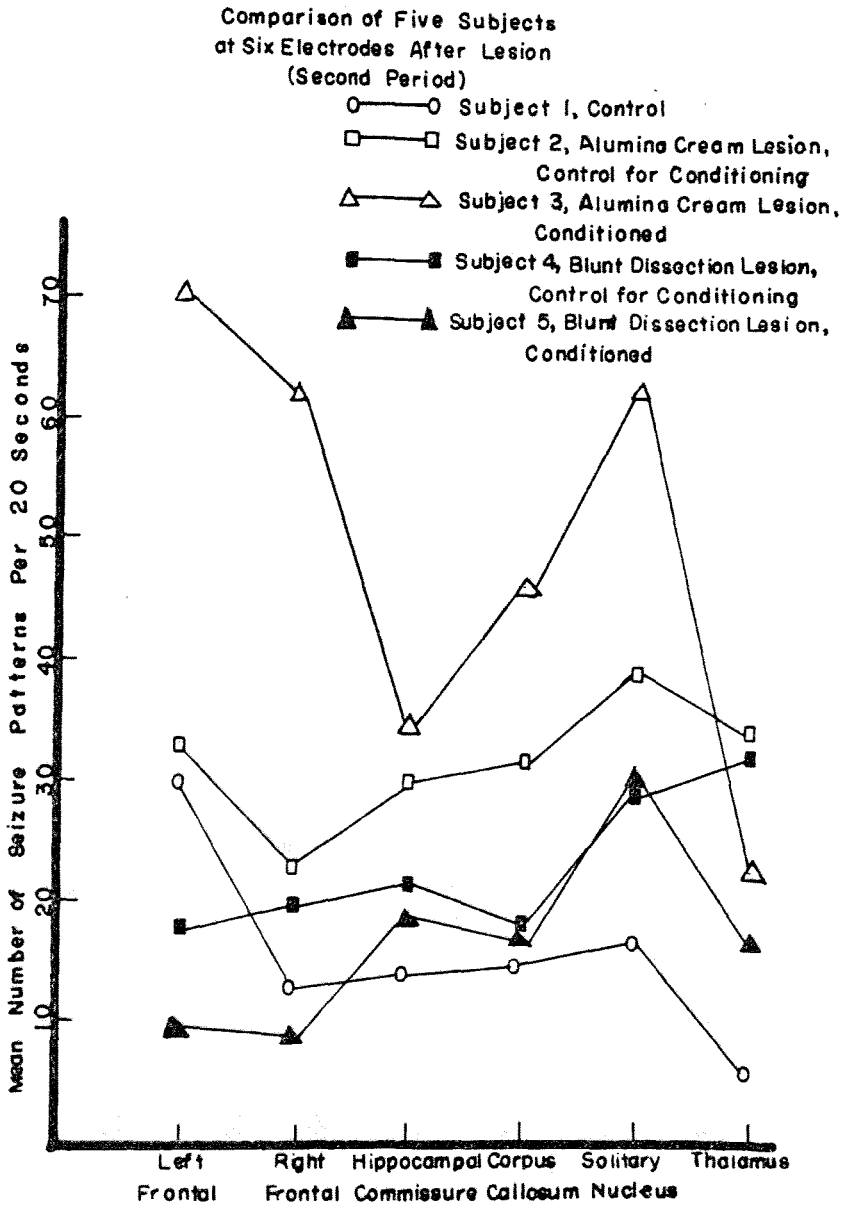


Figure 19. Mean number of seizure patterns as a function of lesion (second period) of six electrodes for five subjects.

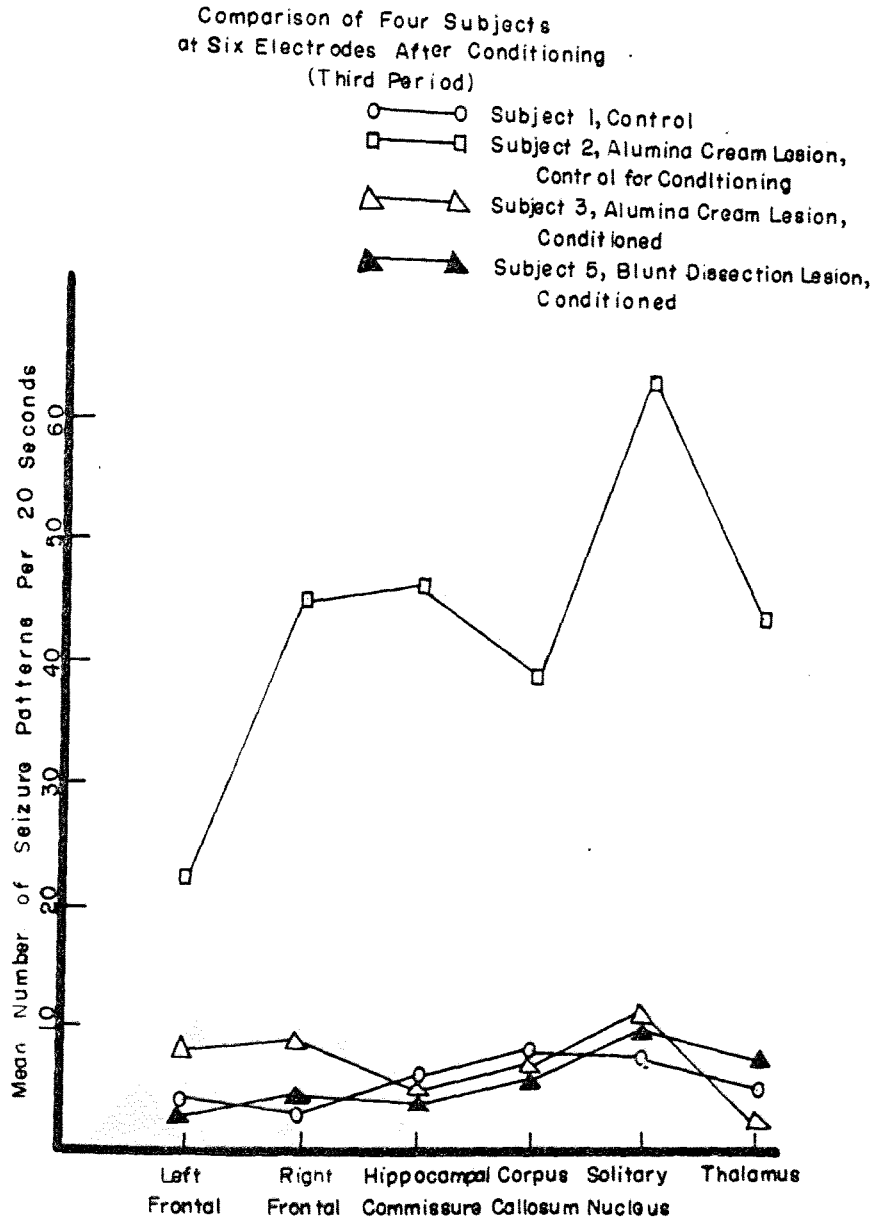


Figure 20. Mean number of seizure patterns as a function of conditioning (third period) of six electrodes for four subjects.

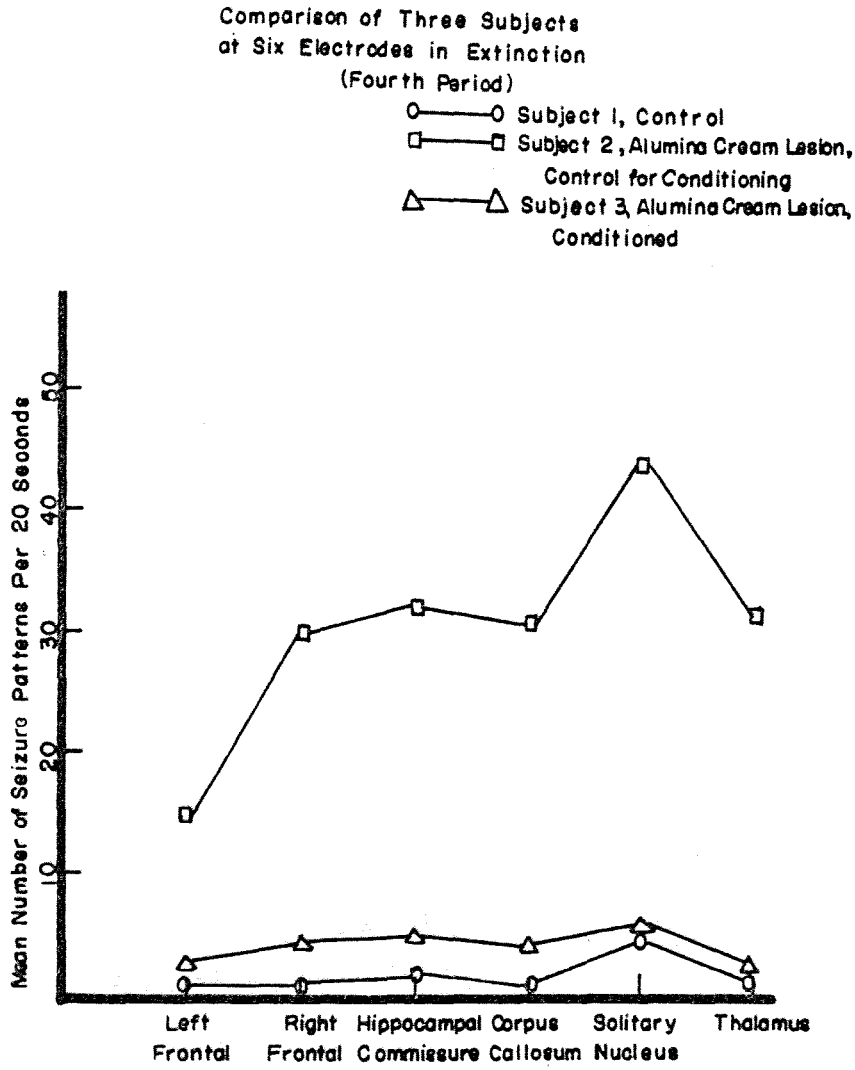


Figure 21. Mean number of seizure patterns as a function of extinction (fourth period) of six electrodes for three subjects.

increase whereas Subject 1 displayed only a slight increase in seizures as a result of the electrodes.

The paradigm of punishment and positive reinforcement of other behavior did suppress the seizures and increase other behavior. This is indicated by the mean seizures in the third period for Subject 3 (See Figure 20). In the fourth period (See Figure 21), there was a slight increase in seizure activity for Subject 3 and then a decrease to a level comparable to Subject 1. During the fourth period, there was a decrease in the number of seizures for Subject 2 but the severity of the seizures increased.

Histology was performed upon Subjects 1, 2, 3, 4, and 5. No neural degeneration or muscle atrophy was observed.

CHAPTER IV

DISCUSSION

The results significantly indicate that a lesion of the vagus nerve at the nodosa ganglia created epileptic seizures and that punishment of seizures and positive reinforcement of other behavior decreased seizures. Because the vagus nerve is the parasympathetic innervation of the heart and respiratory system, these findings are relevant to better understand and hopefully prevent the sudden death of persons diagnosed as epileptic, of persons who are not diagnosed as epileptic but who have disruptions of cardiac or respiratory functions, and of young babies classified as crib deaths, who have the same cardiac and respiratory failures.

Neural degeneration is detected on approximately the 18th day after creation of a lesion. In this study, 18 days was too soon to sacrifice the subjects. By the time the subjects became deceased or were sacrificed, the glia would have absorbed the neural tissue and any indications of degeneration would have been destroyed, which explains why degeneration did not appear in the histological slides.

Just as there were no indications of degeneration and it was too soon to observe atrophy, this may explain why there is often no anatomic explanation of death. In the case of the young 32 year old woman (Webb, 1969), the behavioral manifestations of seizures did not occur until

a few months prior to death and there were no EEG manifestations of seizures. It is likely that she had a lesion of the vagus nerve at least a year prior to her death. The time for detection of degeneration had passed and at least a year was necessary for the atrophy to have occurred and the scar-like tissue to build up.

Fear of the unknown has always motivated man to search for understanding. For centuries, man attributed an epileptic attack to an omen, an evil curse which overpowered the victim. Even today we have not progressed much beyond this state. Epileptic attacks are still referred to as fits, spells, or seizures (Penfield & Jasper, 1954). Today man fears sudden death and many theories attempt to explain it.

There appears to be a similarity between the sudden death of persons diagnosed as epileptics, persons who have not been diagnosed as epileptic but who have disruptions of cardiac or respiratory functions or both, and young babies classified as crib deaths, who have the same cardiac and respiratory failures.

Lesions of the nodosa ganglia may possibly occur during birth. As the baby passes down the birth canal, a great amount of pressure is exerted upon the head and neck. The vagus nerve, especially the nodosa ganglia, is located in a precarious position as it exits from the jugular foramen along with the carotid artery and jugular vein. Since an injury at birth may not appear until the

third decade of life (Penfield & Jasper, 1954), it appears that the degree of assault would determine the time and magnitude of the behavioral manifestations of the seizures. In this study both the alumina cream and blunt dissections created lesions which were accompanied with behavioral and EEG manifestations of seizures. The subjects which received the alumina cream injections displayed a greater number of EEG seizure patterns, but both of the subjects which received the blunt dissections became deceased during the study. This would indicate that the blunt dissection was more severe.

The vagus nerve is a mixed nerve containing afferent roots to the solitary nucleus and efferent roots from the dorsal motor nucleus and ambiguus nucleus (Curtis, Jacobson & Marcus, 1972). Since seizure patterns were recorded from the afferent system, it is plausible that the efferent vagus innervating the heart, lungs, thyroid, etc., was affected. Utilizing an electrocardiogram as well as an electroencephalogram would have been beneficial. Because of the vagal innervation of the thyroid, it would also have been beneficial if larger subjects had been used in this study. The amounts of blood required for laboratory tests on the chemical levels of calcium, thyroxin, nerve growth factor, etc., were more than could be removed from the subjects and allow them to survive. Chemical factors are critical for the normal function of the individual neurons, synaptic transmission and a factor in epilepsy.

A lesion at the nodosa ganglia of the vagus nerve creates a focus at the solitary nucleus, which creates clinical manifestations of epilepsy and are not detectable on scalp EEG. If efferent effects from the same lesion create a focus at the heart, lungs, thyroid, etc., it is possible that cardiac and respiratory failure could occur as exemplified in the Webb (1969) and Hirsch and Martin (1971) studies.

An opposing theory is that of Wolf (1968). He theorizes that by learned inhibition (Pavlovian conditioning), the vagus nerve and the sympathetic system function cooperatively rather than antagonistically to produce a means of death. If this theory is true, there would not be a lesion.

Perhaps the explanation for one seizure (which is apparently no different from previous seizures) being fatal, lies in a theory which combines both physiological and learning theories. It seems more plausible that a lesion of the vagus nerve accompanied with ill-adaptive physiological responses is the answer. Utilizing the punishment-differential reinforcement of other behavior did reduce the number and severity of seizures in this study. The punishment appears to be more effective than the reinforcement. Both the seizure patterns in the EEG and the behavior showed a decrease in seizures. Even though all the subjects which received lesions displayed an abnormal release of energy within the nervous system (seizures), it appears

that experiencing the behavioral manifestations of the seizures was debilitating. The subjects which received the punishment and reinforcement continued to display some abnormal electrical phenomena but were able to control their behavior. The subjects which did not receive punishment and reinforcement appeared to facilitate the physiological response of the seizures. It would appear that persons with vagal lesions can control their seizures with operant conditioning techniques just as well as with medication.

Some epileptics intentionally neglect to take their medication to control their seizures. It appears that when abnormal release of neural energy occurs as a result of a vagal lesion and is accompanied with ill-adapted, learned, inhibitive responses, the vagus nerve and the sympathetic system function cooperatively as a means of death. Rather than avoid or escape from a seizure, the person has learned to facilitate the seizure, becoming more debilitated until death occurs.

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APPENDIX

STATISTICAL TABLES

TABLE 1

Analysis of Variance Summary

Source	df	SS	MS	F
Electrodes	5	2,344.26	468.85	4.39*
Four Conditions	3	19,049.65	6,349.88	59.47**
Days of Conditions	3	7,415.40	2,471.80	23.15**
Subjects	2	24,206.19	12,103.09	113.36**
Electrodes x conditions	15	7,983.81	532.25	4.98*
Electrodes x days	15	2,455.97	163.73	1.53
Electrodes x subject	10	29,948.30	294.83	2.76
Conditions x days	9	19,043.60	2,115.96	19.82***
Conditions x subject	6	26,370.37	4,395.06	41.16**
Days x subject	6	13,151.41	2,191.90	20.53**
Electrodes x conditions x days	45	4,964.88	110.33	1.03
Electrodes x conditions x subject	30	5,482.67	182.76	1.71
Electrodes x days x subject	30	2,850.84	95.03	.89
Conditions x days x subject	18	45,920.03	2,551.11	23.89***
Error	90	9,609.46	106.77	

*$\underline{P}$ <.001
**$\underline{P}$ <.1
***$\underline{P}$ <.5

TABLE 2

Planned Comparisons

Comparison: Subject 1 vs. Subjects 2 & 3.

$q = 10.405^*$

$^*q < .99$

Comparison: Subject 2 vs. Subject 3.

$q = 4.55^*$

$^*q < .99$

Comparison: Left and right frontal electrodes vs. four depth electrodes.

$q = 193.90^*$

$^*q < .99$

Comparison: Electrode at solitary nucleus vs. electrodes at corpus callosum and thalamus.

$q = 366.6^*$

$^*q < .99$

TABLE 3

Mean daily seizure patterns per 20 seconds for Subject 1, Control

Electrodes	Condition: Electrodes				Condition: Lesion			
Left frontal	.65	2.25	31.55	24.05	5.55	33.20	44.85	35.50
Right frontal	18.45	16.50	23.50	33.70	20.70	11.10	11.50	9.10
Hippocampal commissure	10.75	10.50	18.40	30.85	10.75	17.00	17.20	9.45
Corpus callosum	11.75	7.60	5.65	36.00	4.35	22.35	18.70	13.50
Solitary nucleus	.6	0	0	.05	10.85	24.30	17.90	11.75
Thalamus	5.95	7.10	5.85	8.45	9.40	1.75	.45	8.80
	Condition: Conditioning				Condition: Extinction			
Left frontal	4.40	6.75	1.30	3.35	.10	.25	0	.15
Right frontal	.25	3.60	1.5	4.45	.10	.05	0	.20
Hippocampal commissure	4.05	11.95	5.85	2.65	.20	3.65	1.0	.45
Corpus callosum	4.55	10.90	6.25	8.90	.10	.05	.15	1.10
Solitary nucleus	2.60	7.95	7.45	10.05	5.90	6.85	2.35	.30
Thalamus	1.55	6.90	3.35	4.75	.10	.05	0	.30

TABLE 4

Mean daily seizure patterns per 20 seconds for

Subject 2, Alumina Cream, Control for Conditioning

Electrodes	Condition: Electrodes				Condition: Lesion			
Left frontal	19.8	18.45	22.75	27.9	16.2	17.6	32.6	66.20
Right frontal	36.1	29.0	28.3	28.1	14.2	19.25	27.65	30.4
Hippocampal commissure	27.75	19.85	33.35	13.05	27.1	24.40	33.85	36.05
Corpus callosum	24.1	16.1	29.8	14.9	22.7	26.75	37.95	39.65
Solitary nucleus	1.9	25.2	1.2	.55	30.45	30.2	47.35	49.25
Thalamus	1.4	.35	.85	.4	25.1	24.0	46.8	41.45
	Condition: Conditioning				Condition: Extinction			
Left frontal	24.8	20.90	26.55	15.50	14.35	16.30	16.80	13.40
Right frontal	50.05	37.65	59.20	30.95	37.05	45.80	18.35	20.65
Hippocampal commissure	49.3	44.20	55.45	32.05	34.70	38.40	29.60	31.05
Corpus callosum	43.8	35.60	47.20	28.35	32.05	33.15	30.55	30.35
Solitary nucleus	42.15	99.05	74.55	40.15	46.20	49.45	41.25	40.40
Thalamus	46.35	41.25	54.80	29.70	34.0	36.70	30.70	28.90

TABLE 5

Mean daily seizure patterns per 20 seconds for

Subject 3, Alumina Cream, Conditioned

Electrodes	Condition: Electrodes				Condition: Lesion			
Left frontal	5.65	3.05	9.65	12.10	9.45	214.50	30.00	26.90
Right frontal	11.20	7.70	9.95	14.55	6.90	215.75	15.85	8.05
Hippocampal commissure	14.65	8.15	15.65	17.10	9.25	106.80	12.55	12.35
Corpus callosum	14.75	10.85	13.85	24.65	8.45	125.15	36.70	16.60
Solitary nucleus	4.70	2.80	5.30	7.00	16.60	169.30	47.85	20.35
Thalamus	1.05	.50	.05	13.85	13.65	65.30	.05	10.15
	Condition: Conditioning				Condition: Extinction			
Left frontal	5.75	7.45	8.25	7.35	2.05	4.60	1.2	3.2
Right frontal	5.10	8.10	10.0	7.65	2.15	7.25	1.3	4.05
Hippocampal commissure	5.30	6.60	1.35	6.25	5.75	4.70	3.25	2.45
Corpus callosum	2.95	13.15	3.5	10.90	5.25	5.75	2.10	2.55
Solitary nucleus	3.25	15.40	10.75	12.35	3.75	5.40	2.5	4.30
Thalamus	9.55	.05	0	.10	1.9	1.95	.45	.55

TABLE 6

Mean daily seizure patterns per 20 seconds for

Subject 4, Blunt Dissection, Control for Conditioning

Electrodes	Condition:		Electrodes		Condition: Lesion			
Left frontal	15.55	21.10	17.95	16.20	21.25	15.55	16.25	16.25
Right frontal	8.15	13.30	11.55	10.95	22.35	15.90	21.30	18.85
Hippocampal commissure	10.05	21.25	18.20	16.10	21.90	20.35	18.95	23.20
Corpus callosum	13.90	17.20	15.90	19.60	17.85	16.00	17.70	18.75
Solitary nucleus	9.55	19.45	15.55	11.65	32.85	33.35	22.35	23.50
Thalamus	14.15	19.90	27.15	27.30	43.70	34.10	22.60	25.70

TABLE 7

Mean daily seizure patterns per 20 seconds for

Subject 5, Blunt Dissection, Conditioned

Electrodes	Condition: Electrodes				Condition: Lesion			
Left frontal	14.35	10.15	8.15	11.55	4.50	11.40	11.10	8.95
Right frontal	17.76	12.20	6.55	8.0	7.10	9.95	9.20	8.05
Hippocampal commissure	15.95	9.55	7.80	11.45	19.80	19.50	20.05	16.05
Corpus callosum	13.65	8.25	7.30	10.70	12.85	25.50	15.30	14.10
Solitary nucleus	21.85	14.55	9.25	13.20	13.25	40.10	33.15	31.95
Thalamus	21.90	14.15	9.55	14.50	13.60	16.65	17.40	14.50
	Condition: Conditioning							
Left frontal	3.40	2.30	2.10	3.25				
Right frontal	3.50	2.55	3.40	4.30				
Hippocampal commissure	4.80	3.15	3.80	4.35				
Corpus callosum	7.05	5.60	6.50	7.05				
Solitary nucleus	11.80	7,49	8.30	12.10				
Thalamus	7.85	5.90	6.85	7.75				